FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Joint Meeting of the Anesthetic and

Life Support Drugs Advisory Committee (ALSDAC) &

Drug Safety and Risk Management

Advisory Committee (DSaRM)

FRIDAY, JULY 23, 2010

8:00 a.m. to 3:30 p.m.

UMUC Conference Center at the Marriott

Adelphi, Maryland

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I N D E X

P R O C E E D I N G S

(8:00 a.m.)

DR. KIRSCH: Good morning, everybody. Today is day 2 of the FDA and CDER Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee to discuss the issue of REMS. This meeting is now called to order.

For toxic topics as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take

place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunches.

Before we begin, I would like to remind the committee members that we are seeking your individual perspective on the issues that are under discussion, not the organizational perspective of any particular group or special interest. I'd also like to remind all individuals in the audience and members of the committee to silence their pagers and cell phones. Thank you.

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special

government employees or regular federal employees from other agencies, and are subject to the federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found in 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug and Cosmetic Act, Congress has authorized FDA to grant

waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of risk evaluation and mitigation strategies, REMS, for extended release and long-acting opioid analgesics. As a part of the materials for the meeting, FDA anticipates presenting a proposal for a class-wide opioid REMS and will solicit feedback from the advisory committee and public on the components of

that proposal.

The need for adequate pain control is an element of good medical practice. In this context, some persons suffering from pain need access to potent opioid drug products. However, inappropriate prescribing, addiction, and death due to prescription opioid abuse and misuse have been increasing over the last decade. This is a particular matters meeting, during which general issues related to risk evaluation/mitigation strategies for extended release and long-acting opioid analgesics will be discussed.

Based on the agenda for today's meeting, and all financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 (c)(2)(b) to Dr. Knox Todd for serving on an advisory board for an affected firm. His participation in this advisory board may involve targets for analgesic development, including products such as extended release, and long-acting opioids and competing products, and the impact of REMS on these products.

The magnitude of the interest is 5,001 to 10,000 per year. The waiver allows Dr. Todd to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which are posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information office, Room 6-30 of the Parklawn Building. A copy of the statement will also be available for review at the registration table during this meeting, and will be included as part of the official transcript.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the issues before the committees.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Bartholomew Tortella is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Tortella's

role at this meeting is to represent industry in general, and not any particular company. Dr. Tortella is employed by Novo Nordisk.

We would like to remind members and temporary voting members that if the discussions involve any other products, firms, or issues not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committees of any financial relationships they may have with any firms at issue. Thank you.

DR. KIRSCH: We'll now begin the open public hearing.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances, and for many topics, there are a variety of opinions. One of

our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity and courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session, at the advisory committee meeting, the FDA believes that it is important to understand the context of the individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting.

For example, the financial information may include a company's or group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages

you, at the beginning of your statement, to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

For the speakers, I'll apologize ahead of time. I usually butcher up the names pretty well. So when I call your name, you can tell me how it's pronounced correctly.

The first speaker is Nathaniel Katz.

For the speakers, the microphone will turn off at three minutes. When the microphone turns off, I will expect that you'll stop speaking. Thank you.

You may begin.

DR. KATZ: Good morning. My name's Nathaniel Katz. I'm a pain management physician and I'm a former chairman of this committee. I've been working intensively on the problem of pain and prescription opioid abuse for going on 20 years. Since I chaired the first opioid risk management meeting, now eight and a half years ago, somewhere approaching 100,000 people have died of prescription

opioid overdoses and related events.

What have we been doing all this time? Innumerable forms of voluntary education, monitoring, and surveillance, the essence of the current FDA and IWG proposals. You just sat through a day of presentations describing the results of these approaches.

Do you really need any more data to tell you that voluntary education does not work?

I will remind you of the definition of insanity, attributed to Albert Einstein, doing the same thing over and over again, and expecting the results to be different.

The days of prescribers not being trained how to safely prescribe the number one medication in the United States have to be brought to an end by you today. In my view, you need to finally recommend mandatory prescriber training.

The days of millions of patients walking out of the pharmacy with potentially lethal medication and no training on how to keep themselves and their community safe have to be brought to an end by you

today. In my view, you need to finally recommend mandatory patient training.

If you require training and need a verification system in the pharmacy, it has been stated that this would excessively burden the healthcare system. That's incorrect. Over the past year, our group, with some collaborators, has designed, built, tested, and reported on the technical performance and real-world usability of such a system, and provided all this information to the FDA. Time prevents me from describing the details. Suffice it to say that the system works. It's not burdensome. And it's not expensive. And if we can do it, anybody else can do it.

You will hear a number of objections to such approaches. People will complain that these are registries, which are somehow inherently evil. They are not registries. They are databases, just like the databases we are all already in anyway.

People will claim that prescribers will flee from prescribing if they're required to participate in such programs; however, there are ample survey data

that indicate just the opposite.

People will complain that we should not implement anything without evidence. Guess what? There is no evidence. Nobody's been willing to fund this type of research. This leaves you with two choices. You can do nothing and continue to count bodies or you can recommend interventions that make sense and gather the evidence prospectively. That seems to be an easy choice.

You should also know that many other interventions could have been presented, such as tamper-resistant prescription pads, automated prescription monitoring data checks, et cetera.

So my recommendations to you are as follows. First, mandatory training of all prescribers and patients receiving long-acting opioids as part of the elements to assure safe use of the class-wide REMS. We've shown this can be done. After a specified evaluation period, decide whether to expand to the rest of the opioids, and whether to require some additional risk mitigation approaches I listed earlier. When I bump into you all again eight and a

half years, I'd like you to have a clean conscience that you did the right thing.

DR. KIRSCH: Thank you.

The next speaker is Penney Cowan.

MS. COWAN: Hi. My name is Penney Cowan, executive director of American Chronic Pain Association. I want to thank the FDA for their efforts to ensure opioids will be used safely and appropriately by those who must live with pain.

Given the scope of the REMS outline in the report provided by Dr. Rappaport, the American Chronic Pain Association feels that the educational component should focus both on those who use the medications and the general public. Accidental overdose can be reduced by educating people who have realistic expectations about pain-relieving limits of opioids, understand how to use them, and know the importance of keeping them safe.

Opioid agreements would provide a wonderful opportunity for education and communication with their healthcare providers. The general public also needs to know about the risk of opioids. Pharmaceutical

opioids are the second highest reason for death in this country, and the majority of those were from diversion, not from legitimate users.

But people with pain, who are prescribed these medications, use, store, and dispose of them properly, should not be held responsible for the misuse by the general public. If the REMS is to work, we need to focus our educational efforts on broader populations. Messages need to be defined for different populations, from the very young to the very old. They need to convey the importance of taking and storing medications appropriately and also clearly defining the dangers of misuse.

These messages need to be more visible on the public airwaves and the mass media. This campaign will not make the problem go away, but it can save a significant number of people who might otherwise not be aware of the dangers. Unfortunately, there will always be a group who will continue to misuse these and many other types of substances.

While our focus remains on those who use opioids as part of their pain management regiment,

along with other interventions, to allow them to improve the quality of their life and increase function, we must also look beyond this group. If the general public is provided simple, clear messages about the dangers of medications, misuse and abuse can be reduced. Isn't one life worth it?

The American Chronic Pain Association has already begun through patient education, but public education is even more important. We urge the FDA to take the lead in this important work with the help of organizations like the American Chronic Pain Association, who have been the voice of people with pain for 30 years. Thank you.

DR. KIRSCH: Thank you. The next speaker is Mr. Porada.

MR. PORADA: Thank you. By the time this process is over, it'll be about two years. And where have we come? Basically, in a full circle. We started out with a risk map. We changed the colors and we're back to a risk map. Can we really look at ourselves and say that the things that have been proposed are going to change anything? Will some

class labeling or class wording in the Med guide -- will a patient education piece, involuntary training, change outcomes? I don't think so. So I have a couple of recommendations that, hopefully, will be considered so we don't end up here again in two years discussing this.

FDA and industry, which I am happy to have seen, are starting to think about training, not education. My recommendation was going to be focused on training that are linked to specific behaviors.

Second, we need to understand that practitioners will want training. Our group has presented data. Others from California have presented data that show 80 to 90 percent of practitioners will comply with FDA-mandated training.

Third, a lot of organizations say things can't be done. They say practitioners won't participate. They say training can't be validated. A lot of this is opinion. It's not supported by data. And I would think and encourage that data be used to guide any of the decisions that are made here today.

Finally, voluntary training. We talk a lot

about unintended consequences. What are the unintended4 consequences of voluntary training? Perhaps nobody volunteers to be trained. Would FDA be happy with that? Would FDA punish industry because nobody decided to voluntarily be trained?

So in summary, I would say focus on training, not education. There are data available to support many of the arguments that we have been debating over the past two years, and revisit this voluntary training thing, and perhaps, consider a phased-in approach of initially being voluntary, perhaps over six months, migrating to mandatory. Thank you.

DR. KIRSCH: Thank you.

Our next speaker is Ronna Hauser.

DR. HAUSER: Good morning. And thank you for allowing me this opportunity to share the community pharmacy perspective, regarding the FDA's proposal for a class-wide opioid REMS. I am Ronna Hauser, vice president of Policy and Regulatory Affairs at the National Community Pharmacist's Association, and I have no financial interests to

disclose.

NCPA represents America's community pharmacists, including the owners of more than 23,000 community pharmacies. First and foremost, NCPA applauds the FDA for making the process that led to this joint advisory committee meeting a transparent one.

As patient care and safety are a top priority for community pharmacists, we continue to stress the importance of patient access to therapy while safeguarding against potential for abuse and misuse. We do not believe that REMS should interfere with the practice of medicine and pharmacy and also have concerns regarding the potential proliferation of REMS programs.

With that in mind, NCPA does support the FDA's proposed REMS, as it promotes patient safety without restricting distribution or requiring a physician or patient registry. We also agree that the burdensome logistics of registering the nearly 4 million patients currently using long-acting opioids would create a large number of prescribers and

pharmacies who would potentially opt out of the program.

In addition, we applaud the FDA for their decision to not include immediate release products as part of the REMS, as the burden to the system would be too great. The proposed approach represents the most feasible way to more easily implement a class-wide REMS into practice settings, and at this time, we feel that a more robust plan is not warranted.

NCPA supports the FDA's recognition of the prescriber's role to educate patients regarding medication use, storage, and disposal, and the use of a patient information sheet. Though not required by FDA, we also want to encourage that the community pharmacist's role in patient education be considered, and strongly recommend that whatever components of REMS are provided to the patient, via the prescriber, be made known to the pharmacist as well. This continuity of care will attribute to the best outcomes in overall patient education.

We agree with the proposal that patient education should initially occur at the physician

level. At the time of the office visit, the physician can examine patients to determine whether opioid therapy is appropriate and monitor for any signs of abuse.

When the patient visits their community pharmacy, the pharmacist provides valuable reinforcement of the physician's education through appropriate counseling.

Lastly, NCPA would like to reiterate our support for the creation and use of the single FDA-approved document that would be distributed with these products to replace existing written information currently distributed by pharmacies, which will help to decrease the burden caused by the abundance of product-specific medication guides. We appreciate the agency's movement in this direction.

Once again, NCPA applauds the FDA for moving forward with a sensible REMS approach and would like to encourage the FDA to continue to involve community pharmacists in the creation of these programs. Thank you for your time.

DR. KIRSCH: Thank you.

Next speaker is Carlton Brown.

DR. BROWN: Good morning. I'm Carl Brown, president of the Oncology Nursing Society. And on behalf of our 37,000 nurses and other healthcare professionals, thank you for this opportunity to present our views on this important public health issue.

We commend the FDA for seeking to address this issue. We do, however, have serious concerns regarding the proposal. Any opioid REMS should be reasonable and evidence based, ensuring that patients with legitimate need have access to the opioid pain therapies that they and their healthcare providers deem most appropriate.

We believe that any opioid REMS should not result in unintended adverse consequences, such as creating a shift in prescribing behavior that in turn, could diminish quality of life for patients and/or merely transfer the problem to a different group of Schedule II drugs.

Of serious concern is the FDA workgroups' reports and other documents posted on the FDA website,

related to the proposal, repeatedly acknowledged the lack of baseline data and evidence of the effectiveness of many of the proposed interventions.

Specifically, the FDA needs strong baseline data, including more insight into the sources and diversionary paths for these drugs, so that positive and negative changes can be measured over time.

We believe that an additional research should be conducted and urge the FDA to consider a pilot, as it would allow the agency to determine the validity and appropriateness of various interventions and allow for modification and improvements to the REMS before it is instituted on a large scale.

A pilot would also allow the agency to test two versions of the REMS, one focused on long-acting and extended relief opioids and one that also includes immediate-release opioids. This will help insure that the final national REMS employs evidence-based interventions that have been found to decrease abuse, while not adversely impacting those patients who require the regular use of opioids to improve their quality of life.

We also urge the FDA to develop systems for the safe disposal or return of unused opioids for patients and caregivers. Such a program, combined with patient education, should decrease the number of unused opioids remaining in people's homes, where they can be accessed by non-legitimate users. We support the FDA's decision not to require individual prescribers and patients to enroll in the REMS and not to require real-time verification of prescriber training at the pharmacy level.

Patients with cancer-related pain cannot afford the federal government's misstep in this arena. Acting in a deliberate manner, including piloting a new system, and collecting more data will help the FDA to achieve its goal of ensuring that the benefits of these drugs continues to outweigh the risks. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Dr. Gorman and/or Dr. Parks.

DR. GORMAN: Hello. I'm Jack Gorman, the chief scientific officer for Care Management

Technologies, and I have no financial things to disclose. And I thank you for letting me speak today.

As this slide shows, physicians today are caught between the competing goals of ensuring that patients with chronic pain receive access to narcotic analgesics that they need and preventing the misuse of opioids that they prescribe. Current technology provides reliable methods to differentiate between these issues and to guide clinicians to the medically appropriate prescription of opioids.

There is no longer any reason to use outdated global solutions, solutions that in the past have either been Draconian and resulted in decreased access to opioids for those who need them or lacks that resulted in unnecessary prescription misused and accidental overdose.

As shown in this slide, this current technology uses a method called audit and feedback, which has been shown in the literature to effectively influence prescribing behavior. The technology-based implementation of audit and feedback at Care Management Technologies has had significant impact on

improving psychotropic medication prescriptions. Audit and feedback can help both to insure adequate access, and reduce inappropriate prescribing of opioid analgesics.

Missouri Medicaid has implemented the Care Management Technologies opioid prescribing initiative, and found it to be a cost effective method of identifying numerous situations in which opioid prescribing appears to be inconsistent with best medical practice

This slide shows us just a handful of those categories. This information is then fed back to the prescriber on a case by case basis, and will result in fewer bottles of unnecessary opioids landing on medicine shelves in Missouri. With just a small handful of algorithms presented where, you can see two driving principles that should underlie a data-driven solution for REMS.

First, a significant number of patients and prescribers have been targeted for an intervention to address potentially inappropriate prescribing; and, two, this group still represents only a small

percentage of the opioid prescribing ongoing in Missouri.

Consequently, we can target the problem areas without interfering with the appropriate ongoing delivery of care. This is a 21st century digital solution. We use data and algorithms to find and target the problems. We do not expend our finite resources on delivery areas that are not currently of concern. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Will Rowe.

MR. ROWE: Thank you. My name is Will Rowe. I'm the CEO of the American Pain Foundation, which is a patient support organization. I also have no financial interests to disclose. Thank you for this opportunity to comment on the subject of these meetings.

I also want to thank the FDA and staff and leadership for what I saw, and many whom I spoke to, a very thorough and considerate review of the comments that were submitted, and analysis of these comments. And it struck me and many others that the comments and

input that was delivered was taken seriously, and showed up in what was the eventual recommendation.

The proposed REMS recommendation, from our point of view, was excellent in terms of providing and reflecting the balance, that is the goal of the REMS project, which is to do what can be done to curb abuse/misuse/overdose of the use of these medicines, while protecting access for people who need them.

The proposed REMS clearly recognizes the burden and potential negative consequences of mandatory education certification and patient registries. The focus of the REMS is patient and provider education. One of the features that stands out, from our perspective, it's not just provider education and patient education. It's a very focused and simplified version of provider and patient education that focuses very directly on safety.

With provider education, it's patient selection. It's dosing and patient monitoring. There is a plethora of provider education going on out there, but the focus that is contained in this, and reflected in this REMS, focusing on those three

features, I think is an essential and new ingredient in understanding education.

For patients, it is safe use, safe storage, and safe disposal. Again, there is patient education going on out there, but not that which focuses so deliberately on the safety aspects of these medicines.

So I would like to thank the group for putting this proposal together, and the American Pain Foundation stands ready to assist in the implementation. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Betty [sic] Tully.

MS. TULLY: Good morning. Thank you for the opportunity to address this community. I want the record to show that I have traveled here with Chicago with my own funds. And I am not an employee or member of any pain organization. My name is Betts Tully.

I am a formerly diagnosed chronic pain patient who was misprescribed large amounts of opiates. I am not a medical professional, so excuse me if my layman's terms fall short. I am, however, more importantly, part of the unprecedented and tragic

statistics that brings this discussion to your table. I am represented in those horrifying numbers of medically prescribed death and addiction that has occurred over the last decade.

I have been told by medical professionals that I am lucky to be alive. The discussion of overprescribing, as well as inappropriate prescribing by inadequate trained medical community, is not a new discovery for this agency. It was forewarned. An inevitable outcome was predicted and discussed by the FDA committees as far back as 2001. But the only thing that seemed to be of concern was the idea of access. Access to opiates should not be compromised. We heard a lot about access yesterday, and I predict we will today.

Access. When I went to the pain specialist, I was not aware that my number one right was to have access to narcotics. I went to that doctor for help with my back pain. I got little else than narcotics, along with a devastating addiction. I was also not aware that many doctors have as little as 12 hours' education in narcotic pharmacology, yet receive

licenses to prescribe every scheduled drug manufactured and virtually no restrictions on practices. I was not aware that there were very few requirements for a doctor to set up a business as a pain specialist, and that the system to become board certified in the specialty is voluntary. Most of all, I did not know that the majority of doctors get their information of how and when to prescribe opiates from the pharmaceutical companies that manufacture the drugs.

Had I known these facts, I would have declined the so-called access to pain drugs, because I didn't go to a doctor for narcotics. I went to a doctor because I thought a specialist would find a way to relieve my pain and correct my problem.

Some pain patients believe they have a so-called right to narcotics. They are wrong. They have a right to good medical care by a trained and properly informed physician. And they certainly don't have rights that put my health at risk. We have a decade of misinformation and manipulation that needs to be undone.

DR. KIRSCH: Thank you.

The next speakers are Drs. Budman and Zacharoff.

DR. BUDMAN: Thank you very much. I'm Simon Budman from Inflection and NaviPro. The discussion yesterday talked about metrics, and I'm going to be talking about metrics from substance abuse treatment centers. I'll be talking specifically about the NaviPro datastream.

NaviPro was developed with support of $10 million from the National Institution on Drug Abuse, also additional support from founding sponsors Endo Pharmaceuticals and King Pharmaceuticals.

We need to go beyond the issue of measuring knowledge. We need to go look at changes in behaviors. We have a way to measure behaviors, and measure behaviors very quickly, in terms of the outcomes of the REMS. Looking at what goes on for people at substance abuse treatment is very important in terms of measuring how effective the REMS are.

I'm going to show you some data in just a minute. This data comes from the NaviPro datastream

and substance abuse treatment centers. There's about 200,000 cases in that datastream from 600 treatment centers around the country. It's growing by about 1,500 cases a week. The data right now indicates that about 15 percent of patients coming into that system are abusing one or more prescription opioid. About 60 percent of those patients are abusing extended-release prescription opioids.

This is where they get their drugs. They get their drugs from their own prescription. They get their drugs from family and friends, which was given to them or stolen. And they get their drugs from dealers. We believe that an effective REMS will affect the first two areas quite rapidly. Better patient selection will reduce the number of people coming into substance abuse treatment with their own prescriptions, and better storage and disposal will reduce the people who are getting the drugs from family and friends, that are given or stolen. It's unclear what's going to happen with drugs coming from dealers.

We believe that it's crucial to measure

knowledge, but it's incredibly important to be able to measure changes in behavior. And it's incredibly important to be able to do that in a timely way, not wait three years to get TEDS data to see if the program's working. Thank you very much.

DR. KIRSCH: Thank you.

Next speaker is Dr. Dy.

DR. DY: Good morning. I'm Dr. Sydney Dy. I'm an associate professor at the Duffey Pain and Palliative Care Program, Johns Hopkins Kimmel Cancer Center. I'm here to speak for the American Society of Clinical Oncology or ASCO, the world's leading professional organization representing physicians who treat patients with cancer.

Approximately 1.5 million Americans will be diagnosed with cancer this year. One American dies of the disease every minute. ASCO is dedicated to promoting the best interests of cancer patients. We thank FDA for the opportunity to speak.

The management of pain, especially chronic pain in cancer patients, is a critical issue. Many of our patients suffer from pain that would be

debilitating if not for the use of extended-release opioids. Oncologists are experienced with careful prescribing of these drugs. While ASCO understands the public health issue addressed through REMS and supports FDA's efforts, ASCO expressed concerns that appropriate access to these drugs not be denied to cancer patients, and that the process for obtaining these drugs should not be burdensome for physicians or patients.

Representing over 27,000 oncology professionals, ASCO is a unique resource for guidance for policymakers. In its proposal, FDA encourages sponsors to develop prescriber training in partnership with an appropriate independent third party. ASCO has previously commented that high quality educational materials have already been developed, both by our organization and other societies representing health professionals in pain management, in hospice and palliative care, to name a few. We encourage FDA and sponsors to use existing materials and offer our assistance in developing and reviewing new educational modules.

The proposed REMS includes patient education sheets to be developed by the sponsor and approved by FDA. ASCO offers its support in developing these educational materials. Our patient website, cancer.net, offers free of charge, a series of modules and articles written specifically for patients and reviewed by the cancer.net editorial board, composed of more than 150 oncologists, nurses, social workers, and patient advocates.

FDA has commented that it may be more efficient to link physician education to existing DEA registration. This would require new legislation, but would ensure appropriate physician education. ASCO supports this model and suggests that DEA registration be contingent upon successful completion of this educational program with CME credit.

Because sponsor-developed educational programs may not be developed eligible for CME, ASCO strongly encourages FDA, sponsors, and independent third parties such as ASCO, to explore with a CME, possible strategies for meeting both REMS educational goals and CME requirements.

FDA is required to evaluate the effectiveness of new REMS. ASCO is pleased to see inclusion of measures that will address access. Undertreatment is a continuing issue in cancer care and should not be worsened by unintended consequences of new REMS. It's very important to monitor patients' access to appropriate pain management.

A single education product and one assessment plan would be most efficient. This should be a collaborative effort among sponsors, FDA, and appropriate third parties such as ASCO. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Theresa Grimes.

MS. GRIMES: Good morning. My name is Terri Grimes. I'm a nurse practitioner in pain management, associate vice president for nursing in a community hospital, and president for the American Society for Pain Management Nursing. The views I share with you are my own.

Thank you for a thorough and thoughtful review of REMS and for the final report of the workgroups. I support the recommendation to include

all opioids in the REMS process. Everyone should have access to effective pain management that includes a balanced approach toward reducing pain, improve quality of life, and improve physical functioning while promoting safety through education to take medication only as directed to secure and dispose of medication properly, and if side effects, to seek immediate attention.

The National Quality Forums Safe Practices for Better Healthcare 2009 update endorses 34 safe practices. Number 5, informed consent, asks patients or legal surrogates to teach back, in his own words, key information about the proposed treatments or procedures for which he or she is being asked to provide informed consent.

Teach-back is promoted by health literacy experts Dr. Barry Weiss and Joanne Schwartzberg. Dr. Weiss, in Removing Barriers to Better, Safer Care Manual for Clinicians, states, “There’s often a mismatch between the clinician’s level of communication and a patient’s level of comprehension that can lead to medication errors and adverse medical

outcomes."

In 2009, the Deseret News printed that the number of prescription drug-related deaths in Utah decreased by 12.6 percent between 2007 and '08, coinciding with the health department's use only as directed campaign. Information was presented in brief, plain language with bulleted points given for the patient and caregiver to remember.

Teach-back should be adopted as recommended by the NQF and others. Information must be brief and to the point, no more than three to five bullets at a visit. If we want our patients to be safe, we must provide them with information that will be easily recalled. Points should be repeated by the pharmacist during callbacks and built upon at future visits.

More detailed instructions may obscure critical points to remember. Dr. Leonard Paulozzi is cited in a recent interview on unintentional drug poisoning deaths, that 40 percent of opioid prescriptions are written in our emergency departments. Patients are often discharged from hospitals with opioid analgesic prescriptions. These

patients are in need of the same process of informed consent. Please do not exclude hospitals from patient education.

Thank you for supporting appropriate education and training for pain management issues. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Dr. Sidney Schnoll.

DR. SCHNOLL: Good morning. My name is Sidney Schnoll, and I'm presenting on behalf of Pinney Associates who have paid for me to attend this meeting. I'm not appearing on behalf of any of our clients, and the views that I'm expressing today are mine and those of Pinney Associates.

Pinney Associates develops, implements, and evaluates REMS for pharmaceutical developers and manufacturers. We consult for many of the companies in the IWG and worked with the IWG to develop the REMS, and, specifically, worked on the metrics prescriber and patient education subteams.

I'd like to talk, however, about the issue of prescription drug abuse, which is a very old

problem and has been a problem in this country for over 100 years. While it is important for FDA to work to reduce abuse, the results of the agency's efforts alone to curb prescription drug abuse will be limited because the abuse occurs mainly in those who are not prescribed the medications. Because of this, it will be a particular challenge to assess the effectiveness of the REMS, which primarily covers patients who are prescribed the drugs, a completely different population.

The FDA has appropriately taken a position with its REMS that there should be minimal burden on patient access and safety. However, to reduce abuse, the agency should take the lead, as Dr. Jenkins and others suggested yesterday, to develop a consortium of all interested stakeholders. One way to do this would be to resurrect the Interagency Narcotic Treatment Policy Review Board.

The board has not met for many years, even as concerned about prescription opioid abuse has increased. We urge the government to expand the board's remit, to address the issue of prescription

opioid abuse, and invite industry, prescribers, dispensers, law enforcement, prevention/treatment specialists, educators, and most critically patients to collaboratively develop a comprehensive approach to address the appropriate use of prescription opioids.

Industry and FDA cannot do this alone. This is not a problem that will be addressed with simple solutions. Unless an integrated approach involving all stakeholders is implemented, there is no chance in adequately addressing this problem. Thank you.

DR. KIRSCH: Thank you. The next speaker is Dr. Zee.

DR. VAN ZEE: My name is Dr. Art Van Zee. I have no financial disclosures. My comments and references are supplied on a yellow handout sheet out here. In spite of much industry promotion to the contrary, and widespread acceptance in much of the pain management community, evidence-based medicine would show that long-acting opioids are not any more effective than immediate-release opioids but do carry increased risk. These increased risks include inadvertent overdose and deaths, and a much-increased

risk of addiction when abused. This has been one of the loud messages of the Oxycontin story.

There are many concerns that I have with REMS as proposed. The proposal would not affect two significant contributors to the prescription opioid problem. First, industry marketing and promotion. Secondly, REMS as proposed would not impact commercial prescribing; now, for example, highlighted by the south Florida situation where 43 of the top 50 oxycodone prescribing docs in the country are located; wherein Broward County, Florida the 115 pain clinics exceed the number of McDonald's in Wal-Marts combined.

I also have great concerns about the current proposal for the industry to provide REMS education to physicians regarding opioid use. It was the industry's blurring of promotion, marketing, and education that played a major role over the last decade in the prescription opioid problem, and it seems most likely that the public health would not be well served by them providing the REMS education.

I'd suggest the following measures could most effectively impact the prescription opioid

problem. Number one, the requirement for all physicians prescribing controlled drugs to have passed a demonstrated competency requirement on first obtaining a DA license and subsequent renewal of the same.

Two, the requirement for all physicians prescribing methadone to have a unique and separate DEA demonstrated competency. Methadone is a pharmacologically tricky and complicated drug. It's been associated with a greatly disproportionate number of overdose deaths.

Number three, a change in the indications for long-acting opioids, since they are no more effective, but do have significant increased risk in relation to immediate-release opioids.

Long-acting opioids should be freely available to all with cancer or terminal illness pain. Long-acting opioids could be restricted from use in chronic, non-cancer pain, but availability could be preserved for chronic, non-cancer pain patients who have demonstrated that they did not do well on other regimens, and this could be achieved through a

compassionate use program.

So in summary, I strongly feel that leaving REMS as currently proposed with simply physician education and patient education by the industry would fall far short of what is needed. And I must say, in 10 years, I've finished on time for the first time.

[Laughter.]

DR. KIRSCH: Thank you.

The next speaker is Cynthia Kear.

MS. KEAR: Good morning. My name is Cynthia Kear, senior vice president with the California Academy of Family Physicians. And on behalf of the CAFP, we would very much like to thank the FDA, the committee, and the industry workgroup for all of the incredible and thoughtful effort that's been brought to bear on this extraordinarily complex issue.

In addressing this significant health issue, the CAFP believes that continuing education, within the context of continuing professional development, can and should be part of the solution. The education, to be truly effective, and to truly effect changes in clinician performance, should be carefully

planned, comprehensive, cohesive, use multiple educational modalities and delivery systems, embody the best principles in adult learning, be evidence based, and both respect and be tailored to the diversity of settings in which clinicians practice.

But effective education, whether funded by government and/or industry, must include accredited educational providers operating within today's widely accepted industry standards. Beyond effectiveness, this is the case if that education is to be perceived as credible, both by prescribers as well as by the larger community.

Current medical education industry standards provide clear guidelines about the need to establish firewalls between pharmaceutical companies and the prescribers who use their therapeutic agents. As Dr. Kapelow indicated yesterday, given the intricate and unique nature of this situation, flexibility is appropriate. Still, knowing how impassioned the larger debate is about conflict of interest, vis a vis content development and pharmaceutical companies, we would caution all participants to be mindful of

perceptions. Optics are not necessarily correct, but they are nonetheless powerful.

The CAFP is the largest specialty society in the State of California and the largest chapter of the AAFP. Because the majority of patients are treated in primary care by family physicians and other primary care clinicians, CAFP worked with eight other state AFP chapters to design, develop and deploy a survey, in order to invite, in a systematic way, the voice of primary care into this discussion. And I believe that all of you have seen the results of our survey.

With the American Pain Society, the CAFP co-convened a summit of other stakeholders. Those attending stakeholders included clinician leaders and staff of 10 membership organizations that represent virtually all prescribers of opioids. Together, we identified and agreed to a comprehensive library of core competencies.

Understanding that the path forward is not easy, simple, or has sure --

[Microphone timed out.]

DR. KIRSCH: Thank you.

The next speaker is Dr. White-Shim.

DR. WHITE-SHIM: Good morning. My name is Dr. Lynn White-Shim, an assistant director in the scientific activities division of the American Veterinary Medical Association. Our mission is to improve animal and human health and advance the veterinary medical profession.

I'm here to underscore the need for all DEA-registered, licensed veterinarians to continue having access to sustain released opioids to relieve animal pain and suffering. Veterinary use of human-labeled drugs is codified within FDA's extra-label drug use rules.

As the access working group discussed in FDA's REMS proposal, DEA has found that veterinarians represent a very low number of cases of abuse. We also believe misprescribing occurs at a very low level, as veterinarians are used to tailoring specific dosing regimens for individual animals across various breeds and species.

The AVMA appreciates what the FDA's proposed REMS is meant to accomplish. However, the access

working group recommended that any proposed opioid REMS not include requirements or exemptions specifically for veterinarians, and we are unclear what this means for veterinarians.

We still assert that veterinary exemption would be most expeditious, and we ask that FDA to closely consider our request. If exemption is not feasible, it would be best to have REMS specifically tailored for the veterinary profession after current assessments are finalized.

Extended-release opioids that are currently used in animals include fentanyl transdermal patches, oral methadone, and oral morphine. These are used for severely painful conditions in animals. Methadone and extended-release morphine are also especially helpful in zoo animals and wildlife.

We appreciate that FDA also intends to address avoidance of improper sharing and appropriate storing and disposal. Regarding improper sharing, a number of states have already put into place prescription monitoring programs, which allows individual states to detect doc hopping. The AVMA is

not aware of doc hopping in veterinary medicine, as it is less likely, since veterinarians determine how painful an animal is, independent of the client's assessment.

However, it's important to note that the state of Kansas is currently conducting a study to determine whether veterinarians are at risk of doc hopping. The study will conclude in 2013. In the meantime, a number of states require veterinarians to report controlled substance prescriptions.

Regarding appropriate disposal, the AVMA believes law enforcement agencies are the appropriate entities to undertake the safe, environmentally sound disposal of opioids from clients.

The AVMA appreciates the opportunity to provide comments this morning. We welcome the opportunity to serve as a source of information to the FDA, and look forward to continued work with you. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Dr. Burns-Lambert.

DR. BURNS-LAMBERT: Good morning and thank

you for this opportunity. My name is Robin Burns-Lambert, a board-certified anesthesiologist and pain specialist, practicing in Berkshire County, a largely rural county in Massachusetts. I have no conflicts of interest except that my travel expenses today are being reimbursed by Analgesic Solutions.

I am here today because I want to urge you, as passionately as I can, to promote better education of both physicians and patients about appropriate management of pain medication and the risks of their misuse. Opioid therapy has potent analgesic effects, but also carries inherent adverse risks that are not apparent to many patients, or even many practitioners. The safety and efficacy of opioid therapy would be greatly enhanced by an easily accessible, but not easily avoidable education program focused on proper management of pain medication, including a medication safety plan and exit strategy, if drug therapy becomes no longer effective.

Massachusetts PMP data showed us that, similar to other communities around the country, millions of doses of opioid medications are dispensed

to our 130,000 community residents every year. Motivated by the personal and public health risks in those numbers, a group of local physicians, pharmacists, and stakeholders embarked five years ago to strengthen and improve local management of chronic pain and pain medication.

We discovered the most immediate barriers were the great gaps in provider and patient knowledge. The many CME programs that we offered on these topics have consistently been crowded and have created what one community doctor describes as a new community ethic in managing pain and pain medication.

We have heard no suggestion that providers found education on these topics intrusive or unwelcomed. Instead, they were eager for information that instills greater confidence in addressing this often challenging population of medical problems. With that increased comfort, many of our doctors who had stopped caring for chronic pain patients have now resumed that practice, thereby increasing patient access to care.

A REMS feasibility study recently done in

our community tested a short educational program designed to inform patients and refresh physicians' fund of knowledge about opioid therapy. Providers found it enlightening, and patients reported that they appreciated the educational opportunity. It's focused on medication safety.

Our own experience in Berkshire County makes clear that provider and patient education, in an easily accessible format, is an essential patient health and safety tool. Pain management and opioid safety knowledge cannot simply be presumed. The benefits and risks of pain medication are too great to allow essential education about them to be optional or left to pharmaceutical companies alone.

An easily accomplished but mandated educational exercise will reduce barriers to care and lead to a greater fund of knowledge for both physicians and patients, thereby encouraging appropriate physician prescribing practice, and decreased patient-adverse outcomes, as patient safety is our ultimate goal. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Philip Saigh.

MR. SAIGH: Thank you. Good morning. My name is Phil Saigh. I'm representing the American Academy of Pain Medicine. The Academy was founded in 1983. It's a medical society representing over 2,000 physicians who specialize in pain medicine.

In speaking about the use of opioids, the Academy believes that we must balance efforts to curb abuse and misuse with efforts to maintain appropriate access for legitimate patients.

We have four points. First, we believe we must implement and fund a national prescription monitoring program, or a coordinated multi-state effort, with real-time data available to physicians and pharmacists.

Second, we believe the REMS must be established across all classes of opioid medications. Regulating only a specific class will not prove effective and may result in denial of access.

Third, we recommend that the registries be avoided, as these tend to stigmatize the patients that are involved in them. And there's no evidence to

suggest their appropriateness or their success.

Finally, we want to engage experts in the development of education programs, which include comprehensive core curriculum, which span the continuum of all medical education, and which ensure the broadest reach and accessibility.

With respect to this point, I'd like to cite a reference from the findings of a recent study conducted by the Alliance for State Pain Initiatives. The study examined a CME activity that was co-sponsored by the Federation of State Medical Boards, entitled Responsible Opioid Prescribing: A Physician's Guide.

Over 98 percent of the physicians who participated in this study indicated that the guide would be effective in helping them prescribe, communicate with their patients, and be more effective in running their practices. We strongly recommend the adoption of responsible opioid prescribing CME activity as a central prescriber initiative, educational initiative.

In summary, the Academy believes that

balance is essential in successfully addressing the prescription drug abuse problem and the problem of undertreated pain. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Justine Coffey.

MS. COFFEY: Good morning. My name is Justine Coffey, and I'm the director of Federal Regulatory Affairs at the American Society of Health System Pharmacists. ASHP is the 35,000-member national professional association representing pharmacists who practice in hospitals and organized health systems, including ambulatory care clinics, hospital outpatient pharmacies, home care, and long-term care.

I appreciate the opportunity to present the views of ASHP regarding REMS for extended-release and long-acting opioid analgesics, and I have no financial interests to disclose.

ASHP strongly encourages FDA to explicitly exempt inpatient hospital settings from a REMS requirement for opioid drugs. Multiple healthcare providers are involved in the care of the patients in

a hospital.

Through this interdisciplinary care model, there are built-in checks on each of the healthcare providers involved in the patient's care, including nurses, pharmacists, and physicians. Patients do not self-administer drugs, and there is always a healthcare professional in the general vicinity of the patients when the medication is administered.

Furthermore, many hospitals and health systems have decision support systems in place to prevent inadvertent overdoses of medications. Opiates are commonly prescribed in hospitals., and patients respond in varied ways to opiates, and need appropriate monitoring and safeguards, even with standard doses. However, since these medications are so commonly prescribed, physicians understand the associated risks and side effects, as do health system pharmacists.

In the hospital setting, education for prescribers about appropriate patient selection, dosing and patient monitoring will not have a significant impact, since these individuals already

have a deep knowledge and understanding of the risks and side effects associated with opioid use.

Additionally, patient education, including the provision of medication guides and patient education sheets, should not be required in the inpatient setting. Federal regulations require that medication guides be provided to patients at the time of dispensing. Dispensing is the act of delivering a prescription drug product to a patient for self-administration by the patient or outside the licensed practitioner's direct supervision. Dispensing can also be the act of delivering a prescription drug product to a patient by a pharmacist under a lawful prescription. Neither of these occurs in an inpatient setting since the drug is administered rather than dispensed to the patient.

In closing, ASHP strongly encourages FDA to explicitly exempt inpatient hospital settings from a REMS requirement for opioid drugs. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Kevin Nicholson.

MR. NICHOLSON: Good morning, and thank you

for the opportunity to speak with you today. I am Kevin Nicholson, vice president and pharmacy advisor for the National Association of Chain Drug Stores. NACDS represents traditional drug stores, supermarkets, and mass merchants with pharmacies. Our more than 150 chain member companies include regional chains with a minimum of four stores to national companies. Our members fill more than 2.5 billion prescriptions yearly, which is more than 72 percent of annual prescriptions in the United States.

We are pleased to have this opportunity to address FDA's expert advisory committees, that you consider FDA's proposal for a class-wide opioid REMS. As FDA recognizes in the Federal Register notice for this meeting, patients suffering from pain need access to potent opioid products. But also, we must address the growing problem of inappropriate prescribing, addiction, and death due to prescription opioid abuse and misuse.

With this in mind, NACDS supports the measured approach to REMS that FDA appears to be embracing, as evidenced by the FDA's proposal for the

class-wide opioid REMS. FDA must carefully navigate between mitigating the risks of these medications while also not negatively impacting patient care.

We are pleased that the proposed REMS for the long-acting and extended-release opioids follows the advice of stakeholders that emphasizes caution and deliberation over speed. Take time to develop the REMS and allow for stakeholder input to prevent negative consequences.

We have met with FDA officials and provided written commentary on numerous occasions concerning this proposed REMS, as well as the development of REMS policy in general. In the past, as we do today, we strongly encourage FDA to establish REMS in a step-wise fashion. In other words, first establish baseline elements that are expected to address the main concerns that FDA feels necessitates the REMS. If FDA determines that they are not effective, then consider moving on to additional elements.

As a scope working group has noted, prescribers are privy to the most personal information about patients. They can use this information to risk

stratify and make a decision whether opioid treatment is appropriate for a patient. Prescribers can decide to discontinue opioid therapy or refer patients for treatment if addiction develops. As such, we agree with FDA that prescriber involvement is critical to the success of this REMS.

In closing, we thank FDA for moving cautiously. We believe that FDA is taking the correct approach, which should lead to FDA achieving its goal for this REMS. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Dr. Marcie Bough.

DR. BOUGH: Good morning. My name is Marcie Bough. I'm a pharmacist and director of Federal Regulatory Affairs for the American Pharmacists Association, APhA. APhA is the first established and largest professional pharmacist organization, representing over 62,000 members who provide care in all practice settings.

APhA has been actively involved in REMS discussions with FDA and other stakeholders over the last few years. As outlined in APhA's 2009 REMS white

paper, included in the committee member's background materials, we continue to advocate for a standardized system-based approach that is feasible and scalable to accommodate the growing number of REMS programs.

Specific to FDA's proposed opioid REMS, APhA appreciates FDA dedicating time and resources necessary to evaluate and implement the program. Additionally, we support provisions, balancing patient safety, access, and risk management, limiting burden on the healthcare system, and limiting unintended consequences, utilizing FDA's Safe Use Initiative to complement the REMS program, and utilizing accredited continuing education materials that include specific information on safety risk the REMS is designed to mitigate and outcome measures that capture practice changes.

Yesterday, the committees discussed the impact of education on practice and the benefits of public health. While not specific to pain, I want to highlight that pharmacy continues to build on the successes of immunization education. By 2010, nearly 115,000 pharmacists have been trained to immunized and

have administered over 14 million vaccinations this past flu season.

Turning to recommendations, while the proposed REMS does not include specific requirements for pharmacists, APhA recommends the following improvements to strengthen the program. One, first ensure that pharmacists receive outreach and educational materials about the REMS program. Pharmacists often discuss REMS information with prescribers and patients, and need to be aware of the program elements.

For example, pharmacists may have patients arrive to the pharmacy with a patient information sheet they receive from the prescriber. Also, pharmacists may wish to utilize the tool and review the educational materials for their own benefit, as well as with their patients.

Second, we recommend recognizing the role that pharmacists play, as the medication expert and safe medication use and patient care as an important part of the healthcare team.

Finally, you heard yesterday, nearly

76 percent of extended-release opioids are dispensed through community pharmacies, all of which include a pharmacist, an important part of patient safety. With appropriate time and resources, pharmacists can further improve public health and education. We challenge FDA and sponsors to continue to evaluate the potential impact, need for an ability to compensate for counseling services at the point of dispensing as part of a REMS program.

In closing, we look forward to continuing to work with all stakeholders as we --

[Microphone times out.]

DR. KIRSCH: Thank you.

The next speaker is Dr. Rosemary Orr.

DR. ORR: I have a slide presentation. I'm a doctor from Seattle and from the University of Washington. I'm also the mother of Robin, who died of an Oxycontin overdose in 2006. These are the names of others of his friends who have died, friends or children of parents I know in Seattle, in the subsequent three years.

Because, as an anesthesiologist, I don't

prescribe long-acting opiates, I had to find out what I could about Oxycontin. I was astonished to find out how widespread the abuse of Vicodin and Oxycontin are in our area. Two friends of my son died in the two years after he did. The stepdaughter of a colleague died in 2008. And another colleague has a son who's been in and out of rehab for his addiction. I also know of two of my son's friends who continue to have problems with Oxycontin addiction.

This is the latest data from the Washington State Department of Health. And as you see, up until 2008, and as you know from yesterday, deaths continue to increase; hospitalizations also.

I think that education of the medical community and the public is key to safe use of prescription opiates. The pharmaceutical companies have a very different mission from ours, to make money for their shareholders. We as physicians must read about evidence-based efficacy in the medications we prescribe, and we must use them safely.

We were told in 1995 that pain was being undertreated, and we responded as we could. I believe

that this resulted in widespread overuse of opiate drugs. I use every opportunity to discourage colleagues and dentists from giving out large amounts of post-operative opiates, which may remain in medicine cupboards.

I've been a doctor for over 40 years. For most of my career, I've worked to relieve the pain of surgery and to provide comfort to children and their families. I'm not against the treatment of pain; however, there is more we can do as a medical community and society to encourage healthy lifestyles and to use complimentary options for treatment of pain and other conditions, in addition to drugs.

I encourage this committee to work to control inappropriate prescribing, and inappropriate marketing of these drugs. I finish with a quote from my son. "Mom, Doctors are the biggest drug pushers in this country." And I wish I had listened to him. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Rebecca Kirch.

MS. KIRCH: Good morning. I'm Rebecca

Kirch, associate director of policy for the American Cancer Society Cancer Action Network. While many effective medicines are available to relieve cancer-related pain, significant pain assessment and management deficiencies are consistently reported in the clinical settings where patients and survivors get their care.

The medicines that are the subject of this particular REMS are very important to people living with cancer-related pain to ease their suffering and help maintain their quality of life. As such, we are immensely grateful for the time and care that FDA devoted to this REMS process, particularly staff's consistent efforts to hear and use stakeholder input along the way. We're pleased that much of the input is reflected in the balanced background materials that are in front of the joint committee for this meeting.

I'd like to focus my brief comments this morning on the importance of continuing our work together to articulate specific and meaningful access measures as part of this REMS, to ensure this initiative does not inadvertently impede patient care

and that we also have an appropriate and timely agreed-upon exit strategy at the ready, if we determine that it does cause harm.

I know and am reassured that this topic of determining appropriate access measures to help evaluate the impact of REMS has been an area of intense discussion within FDA. Research findings from a prescriber's survey, that ACS CAN helped coordinate across the palliative care professional community last year, made clear how regulatory activity, in the absence of meaningful stakeholder involvement, in that case, FDA's unapproved opioids initiative, can cause real harm to patients very quickly.

Most significantly in that study, it included more than 2,600 responses from all 50 states, while more than half of the responding doctors and nurses confirmed that they experienced shortages and availability of important pain medicines, and more than one-third indicated that they were forced to change medications for stable patients as a result.

Given that learning experience, we know that evaluating the impact of this particular REMS, on

prescribing and patient care, and doing so at regular intervals, will be critical to the success or failure of this initiative.

Our hope moving forward is that FDA will continue to work closely with stakeholders to determine and agree on clear access measures, and the timeline for implementing them, to gauge how the REMS is doing, and how patients are faring.

ACS CAN stands ready to work with FDA, its advisory committees, and our many partners in the health professional community to help determine and agree on the most useful and appropriate measures and timelines to use regarding REMS and patient access, as well as the research process we use to implement those measures, to ensure continued access to essential pain medicines that promote better pain management and improved quality of life. Thank you very much.

DR. KIRSCH: Thank you.

The next speaker is Dr. Jacqueline Watson.

DR. WATSON: Good morning. My name is Dr. Jacqueline Watson, and I'm the executive director for the District of Columbia Board of Medicine. I have no

financial interests to disclose.

On behalf of the Federation of the State Medical Boards, I am pleased to speak in support of the FDA's proposal for a class-wide REMS for long-acting, extended-release opioids.

The Federation represents the 70 state medical and osteopathic boards in the U.S. territories. These boards are responsible for regulating the practice of more than 750,000 physicians in this country. The vast majority of the boards also license physician assistants and a variety of other licensed health professionals.

Since 1998, the Federation has worked with major stakeholders, including leading pain and addiction specialists, medical professional organizations, state medical boards, and state and federal law enforcement to develop and promulgate guidelines for the safe and effective prescribing of opioid analgesics.

The resulting model policy for the use of controlled substances for the treatment of pain has been adopted, in whole or in part, by 41 state medical

boards, including the District of Columbia. In 2007, the Federation Research and Education Foundation published the handbook Responsible Opioid Prescribing: A Physician's Guide. This publication translates the model pain policy into pragmatic and effective strategies for physicians to apply in the clinical setting.

The practical guide, authored by Dr. Scott Fishman, chief of pain medicine at UC-Davis, provides physicians effective strategies for reducing the risk of addiction, abuse, and diversion of opioids that they prescribe to their patients in pain.

It has been distributed by 21 state medical and osteopathic boards to more than 150,000 physicians, other prescribers, and physicians in training. State medical boards have enthusiastically endorsed the book and continue to seek resources to support their distribution of the book. Boards have communicated to their licensed physicians that use of the book will help them safely and more effectively manage their patients' pain. This book is accredited for 7.25 Category I hours of CME education and can be

used to fulfill state medical boards' CME requirements for license renewal.

The American Academy of Pain Medicine and the Alliance of State Pain Initiatives submitted written comments on July 8th, urging the FDA to designate the responsible opioid prescribing CME activity as a mandatory element of all prescriber education curricula in REMS for long-acting opioids prescribing.

The FSMB supports the AAPM and ESPI proposal, and working with the ACCME, the University of Wisconsin, and/or the University of Texas, Southwestern Medical Center, the Federation has the capacity to revise and expand the CME activity to ensure the content reflects the FDA's expectations.

In conclusion, the Federation supports --

[Microphone times out.]

DR. KIRSCH: Thank you.

The next speaker is either Dean Hart or Mr. Mohler.

MR. MOHLER: Good morning. My name is David Mohler, and I'm speaking on behalf of NanoGuardian,

which is an on-dose pharmaceutical security technology company. I am a lawyer for NanoGuardian, and that's my interest.

NanoGuardian appreciates FDA's including multiple stakeholders in the discussion of opioid-specific REMS, which was brought to the forefront, given the need to curb rising misuse and abuse of these medications. However, the epidemic of controlled substance abuse has evolved well beyond the educational problems that may exist between physicians, pharmacists, and patients. And at least in the early days of the REMS discussions, the illegal diversion of opioid analgesics was not only referred to by the agency itself as a surrogate for abuse but also referred to as a serious issue that would be included in the REMS.

While it's understandable that the agency has decided to focus its efforts on improving the education of the people who belong in the legitimate patient pharmacy and doctor system, there remains a looming issue, which will continue to drive the escalation of misuse/abuse of these products, the

criminal diversion of these medicines.

So while we at NanoGuardian are extremely grateful for being included in the process and support greater education, we're disappointed that the agency has not recommended using all resources available to tighten the supply chain to avoid diversion.

These resources include new on-dose technologies which can help law enforcement and the agency determine the source of illegally diverted opioids, such as the 100,000 Oxycontin found in a hidden compartment of a car stopped in North Carolina in April of 2009.

Even without packaging, on-dose technologies can help to determine the source of these products. On-dose and other technologies can aid law enforcement in determining the true source of these illegally diverted medications, and thereby reduce diversion of products throughout the nation.

Finally, we wanted to make a small comment aimed at correcting the record from the process. In the agency's comments about on-dose anti-counterfeiting technologies and diversion

technologies, the agency noted that wholesalers argued that requiring manufacturers to use on-dose technologies to aid and track and trace would put a burden on wholesalers. While some technologies do require significant downstream supply chain participation, technologies such as NanoGuardian's nanoencryption technology can work very effectively without any downstream supply chain partner participation. These technologies can provide very meaningful data to law enforcement and regulators to fight in their fight against diversion, primarily through the activities of manufacturers of these agents.

Thank you again for allowing NanoGuardian to participate. We look forward to seeing you again as the agency tackles the issue --

[Microphone times out.]

DR. KIRSCH: Thank you.

The next speaker is Fred Wells Brason.

MR. BRASON: Good morning, and thank you for the opportunity. I am here through the Chronic Pain Initiative in Wilkes County, North Carolina, where we

all know that the average of overdose deaths for the United States is 10 per 100,000. In Wilkes County last year, we had 46 per 100,0000.

We address this issue through the Chronic Pain Initiative, through the Medicaid authority in North Carolina, to work with the physicians in our community to determine the best way to address the overdose issue. Because of what we did with the Chronic Pain Initiative, which that study has been submitted to the FDA through the evaluation of Wake Forest University, it shows that when prescribers were working with their patients through the prescription monitoring program, they were able to find out that those patients that were doctor shopping.

When they had in their hands the physician contract pain agreement, they found that they were empowered to work with their patient, and the patient was empowered to discuss with their doctor the prescription and the need for possibly more pain medication. So they found the number one thing that they could use was that pain agreement that they had with their patient. In that study, that was found.

Working with them and working with the physicians in that, we found that 70 percent of the physicians in Wilkes County were utilizing the prescription monitoring program. The statewide average is only 20 percent. So that showed that our physicians were using what they could to work with their patients. And what we found between 2008 and 2009, the scripts that were appropriated to those that died from an accidental overdose -- which was 75 percent of those overdoses, meaning 25 percent did not have any script at all. The 75 percent that did have a script within two weeks of their death, that was attributable through the toxicology screen for that death that had occurred.

Those 75 percent, 75 percent of those, in 2009 got their scripts from outside of Wilkes County. The previous year was only 15 percent. So what it showed was that the access to the illegal use of the prescription drugs had been met, because the physicians were doing what they needed to do. They were using the pain contract agreements, the emergency department was limiting the doses of what was being

prescribed, and they were looking at the prescription monitoring program to determine whether the patient was doctor shopping, and illegally using the prescriptions that they were trying to write.

So in that, we found that the community could come together. The community could provide education to the community. The individuals were instructed to lock up their medications, find a lockbox if they can. And that's another issue, that lockboxes aren't readily available. They had to go to Wal-Mart to get a cash box. But we've done that in the community to limit the access, because in North Carolina, 350 million doses of narcotic scripts were prescribed in 2009 for 9 million people.

So that's a lot of pills that are on the street. So the community education, the physician education, the patient education has made a difference in Wilkes County, as is shown through the Wake Forest evaluation of our project. Because we're still having the deaths, then we encourage FDA and others, as the North Carolina Medical Board did, was to prescribe --

[Microphone times out.]

DR. KIRSCH: Thank you.

Our last speaker in this session is Seddon Savage.

DR. SAVAGE: Good morning. My name is Seddon Savage. I'm a physician in pain medicine and addiction medicine. I currently serve as president of the American Pain Society, and I am speaking on behalf of APS.

APS is a national community of basic science and clinical researchers, and of clinicians across a broad spectrum of practice, physicians, nurses, psychologists, pharmacists, and others. APS thanks the FDA on its careful consideration of the comments of diverse stakeholders over the past two years and in work towards achieving a balanced approach to REMS.

We believe that REMS should ideally support improved opioid prescribing by clinicians, safe and effective use of prescribed opioids by patients, deter misuse by patients and the public, and avoid significant interference with appropriate prescribing for pain.

We believe that FDA has listened and in

large part achieved this through a combination of requirements for patient education and physician education, and very importantly, for assessment of the outcomes, the impact on both misuse, diversion, abuse, and on access to treatment.

Moving forward, APS stands with multiple partners ready to actively assist in design and implementation of REMS as helpful. With the California Academy of Family Physicians, we convened earlier this summer, a consortium of professional organizations in primary care, pain medicine, and importantly, addiction medicine, that included physicians, nurse practitioners, physician's assistants, pharmacists, prescribers, and dispensers, national organizations to reach consensus on core competencies for safe and effective prescribing of pain. Those competencies have been submitted to the docket, and a list of the organizations involved.

Collectively, these organizations have vast experience in education, training, and most importantly, implementation of practice change. We need to move beyond education to effective change in

practice. This will involve diverse and multi-modal approaches. Academic detailing may be a very valuable one of them, using technology as outreach to accomplish this.

Over the long run, clearly REMS alone is not a solution. We need public education, but probably most importantly, we need better training in the spectrum of approaches to effective treatment of pain; not just opioids, but pain treatment and understanding of pain in the core curriculum of physicians, nurses, pharmacists, physician's assistants, and others who treat patients with pain, in the core training. We will only solve this problem with that and with training in addiction medicine, which is the other side of the challenge that we're --

[Microphone times out.]

DR. KIRSCH: Thank you.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the

committee, as well as the public comments.

It's now time to take a 15-minute break. Our clock says that it's approximately 9:30, and we will reconvene at 9:45. Thank you.

(Whereupon, a recess was taken.)

DR. KIRSCH: The meeting will reconvene now. The plan for the next section of the agenda will be, first, two clarifying presentations. We will then go back to the list that we had for members of the committee to get clarification of issues from yesterday and from today. It's important to note that, although this portion is open to the public observers, public attendees may not participate, except at the specific request of the panel.

So the first presentation we're going to have is by Laura Governale. And she had a number of questions given to her yesterday, and my understanding is that her presentation today will hope to try to clarify some of the issues that the committee had yesterday. Copies of Dr. Governale's presentation have been given to members the committee, and we will post them on the website after the meeting.

DR. GOVERNALE: Good morning. I'm here today to address a few of the questions that were raised yesterday. And one of them was about the cost of promotional spending for extended-release and immediate-release opioids. Now, these databases are used primarily by the Division of Drug Marketing, Advertising, and Communications, so they're the real experts with these data. So perhaps, if any of them are in the audience, they might want to come up and add to this.

So what we're looking at here is the cost of professional promotional activities for extended-release opioids from the years 2005 to 2009. And it's been kind of sporadic in the recent years. But for year 2008, there was about $28 million spent, but in year 2009, it's gone down to about $15 million.

The cost of promotional spending, it shows a cost of advertising, journal promotion, and also the cost of contacts, which is basically going to physicians' offices by the sales reps.

The next slide shows the total cost of promotional activities for immediate-release opioids.

And it was at its highest point with $34 million in year 2005, but in year 2009, it's gone down to about $12 million. And in this case, the professional promotional spending included cost of contacts, journal promotion, and retail value of samples, which was not included in the extended-release promotional activities.

So moving on, I also wanted to address the questions about the number of unique patients receiving these individual extended-release opioid products. And the trends were pretty similar to what was shown for the dispensed prescription slide. So the pink bar represents the extended-release oxycodone products, and the lighter blue bar represents the transdermal fentanyl products. And the darker blue bar represents extended-release morphine products. And the purple bar represents patients on morphine in the last couple years. The brownish bar represents the extended-release oxymorphone products.

If there are no further questions, I'll end here.

DR. KIRSCH: Thank you.

The next item is one of the members of the committee had questions yesterday and was able to gather some data, which we are going to allow him to present. Dr. Wolfe has got two slides.

DR. WOLFE: This was discussed very briefly yesterday, and Dr. Van Zee mentioned it again, that one of the problems or worries about REMS is not the program itself, but that it could easily be overwhelmed entirely by various kinds of marketing promotional activities.

This is a summary. The data are from drug topics, which is a random sample of thousands of retail pharmacies and prescriptions filled in a given year, in millions. And the point of this is to connect the marketing activities of Purdue -- and I'm afraid the deadly elephant in the room is not necessarily the present Purdue people, because I have no reason to think that they were involved in what happened back when. But the company was convicted of criminal activity. And it was based on what they did between the time when the drug was first marketed and the end of 2001. And what they did is overstate the

benefits, understate the risks. And the predecessor of what we're talking about here on extended, long-acting opioids is a risk management program that the FDA and Purdue agreed upon in 2001.

As you can see in the upper left-hand corner of the slide, Purdue was supposed to stop false marketing claims, and they adopted a risk management plan. Somehow or other, after this was adopted, they kept selling huge amounts of Oxycontin. And in the beginning of '03, the FDA wrote them a strong warning letter about what they had done, in clear violation of the risk management program.

This is a letter January 17th, '03 from the FDA to Purdue. In fact, it was to one of the people who pleaded guilty to criminal charges himself.

"Your journal advertisements omit and minimize the serious safety risks associated with Oxycontin and promoted for uses beyond which have been proven safe and effective. Specifically, your journal advertisements fail to present, in the body of the advertisement, any information from the box warning," and so forth; grossly overstate the safety profile of

Oxycontin.

So in the middle of a period of time where they are, A, under a risk management program, and after the justice department, a year earlier in 2002, had begun their criminal investigation, their investigation of the company, they were still doing things to help to sell their drug.

It's interesting this morning in this discussion, people mentioned dealers, that the REMS program doesn't affect dealers. Where do the dealers get their pills from? I think maybe a small amount may be stolen, but they are buying them from other people who are needy, financially, who get prescriptions written and sell them.

The point is that a huge amount of this drug has been in traffic. And in May of 2007, the company pleaded guilty, was convicted by the U.S. Department of Justice; paid $600 million to settle criminal and civil litigation, and signed a corporate integrity agreement with the Office of Inspector General and HHS.

We have been trying to get what has

happened, the progress of this agreement. I hope the FDA has it. I raised this a couple years ago. We've gotten a copy, 90 percent of which has been redacted. We are very eager to see what has happened in this agreement that the company made, having been caught once again for earlier activities.

The summary of this slide is there's been -- in terms of Oxycontin itself. There's generic oxycodone available. This is just Oxycontin itself. There's been a huge increase, tripling, since the year when the company pleaded guilty to criminal charges in a number of prescriptions.

The next slide shows the same thing, in terms of retail sales. This is again, drug topics. The company gets, not obviously all of this -- probably a quarter, a third, but the amount of money that they have gained since the criminal conviction, and sales of this drug far exceeds the amount that they paid. I debated the U.S. attorney on the NewsHour after this conviction, arguing why did no one go to jail, and why did the company pay only money under activities through the end of 2001.

Summary is we've got to pay huge attention to marketing promotion. This includes the funding of a large number of pain societies, some of which testified this morning. The individuals who testified themselves have no reason to think they got money from the company. But certainly, many pain societies -- this was in the 70-page indictment by the U.S. Justice Department, many of these pain societies were funded by Purdue, and probably other companies.

So we have to pay attention to this. This company seems to have bounced back since, and it was convicted criminally, sold more drugs, Oxycontin, and way more prescriptions are in there. The figures that were given were something like 7 or 8 million prescriptions in 2009 of all extended-release oxycodone, of which the majority is Oxycontin.

So I'm very worried about this. I'm sure I'm not the only one that's worried. And I just think that it needs to be part of the discussion. Even though we're focused on, as we should be, REMS, these kinds of efforts can just swamp out everything in REMS unless these companies, any company that does this, is

properly penalized, which they were not the last time. And people who have engaged in criminal activity actually go to jail as opposed to paying out of their own pockets, which three of their officials did, $30 million or so, but didn't have to go to jail.

We're not going to have enough deterrent for this kind of activity. This is another sort of deterrent of the industry. Thank you. I'd be glad if there are any questions at all on this.

DR. KIRSCH: Yesterday, there was a number of questions related to advertising. And it's my understanding that FDA has made available Tom Abrams.

Is Tom Abrams here? I'd ask him to come to one of the microphones, and I'll allow members of the committee to ask Mr. Abrams. Mr. Abrams is in charge of advertising for FDA.

Are there questions for Mr. Abrams? Dr. Farrar?

DR. FARRAR: I guess one of the things that would be important for the committee to understand is the authority that the FDA would have with regard to the implementation of warning labels or other things,

with regard to the opioids. And it's very clear in the television advertisements that they have to run through the litany of potential issues. I don't think I've seen an advertisement for opioid on television for quite a long time.

But I wondered what the authority is in terms of the paper and advertisements and the brochures that are produced, and so on, if the REMS was approved and there was some need to place a box warning or something else that says, "Potential for Abuse," et cetera.

MR. ABRAMS: Hello, everyone. I'm Tom Abrams, director of the Division of Drug Marketing, Advertising, and Communications at the Food and Drug Administration. Our authority would extend to all promotional materials. That would include TV advertisements, any other materials directed to consumers and patients, as well as healthcare professionals.

Specifically, with your questions, the regulations would require a fair balance of risk information. That would include serious warnings,

including the box warnings, which are in the opioid labeling. It would also include elements of the REMS, which would be put into place. That would be one of the requirements that the companies would have to adhere to.

DR. KIRSCH: Sid?

DR. WOLFE: Tom, this question was asked yesterday, and you weren't here, and I think you can probably answer it now.

With the REMS now having been part of FDA law through the 2007 FDAAA, do you have any additional authority that you did not have now, to impose sanctions on companies, specifically in the area of -- well, in this case, it's the opioid REMS. But do you have any more authority now than you had before, in terms of fining or any other sorts of sanctions against companies?

MR. ABRAMS: One of the new authorities that we have in place, apart from FDAAA, is the Food and Drug Amendments Act of 2007. That gave us the authority to impose civil monetary penalties on manufacturers for misleading direct-to-consumer

advertisements. Most of the promotion is directed to healthcare professionals, I note.

However, our existing authorities include issuing regulatory warning letters and untitled letters, as well as seeking injunctions, and seeking seizures if necessary, as well as working with the Department of Justice. The testimony before referenced a case that the Department of Justice worked on and imposed on the manufacturer of Oxycontin. FDA was very intimately involved in the investigation and work-up of that case.

DR. WOLFE: Just a quick follow-up question, which is, yesterday, when this was raised, someone said, and I guess you've confirmed it, that the 2007 FDAAA did not confer authority on you to impose civil monetary penalties for journal advertisements.

The warning letter that you all sent in 2003 to the company was for a journal advertisement. And so you're saying that because that wasn't direct to consumer, you do not have any authority to impose civil monetary penalties on journal ads or any other professional advertising; is that correct?

MR. ABRAMS: The civil monetary penalty provision that was included in FDAAA is for direct-to-consumer advertisements that would appear in consumer magazines. It would not include journal advertisements appearing in medical journals.

DR. WOLFE: Thank you.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: Thank you. I think it might also help the committee, perhaps, if you could explain a little bit as to how launch materials or advertising's actually reviewed, because I think there's some parallels to some regard with how the safety data is being discussed, in terms of core.

What I'm thinking there is, it's my understanding that a company, when they're getting ready to launch, they'll provide what would be their launch advertising so that it's checked against what the label is, and that it's representative of what the full launch materials will actually be, and that the company then has the ability to execute that message, if you will, in multiple media formats.

So maybe you could explain that process.

And what is the process then for self-regulation of when someone may be veering off in the execution? The content may be there, but really, the delivery of the message, the art of the advertising, and how that kind of comes to your attention.

MR. ABRAMS: There's no requirement for most drugs to submit their draft promotional materials beforehand. The law is clear that all promotional pieces have to be submitted to the agency at the time of initial dissemination. We receive about 76,000 promotional pieces a year, just to give you an idea of what comes in.

One of the exceptions is for drugs approved under Subparts E and H, the accelerated approval provisions. In those materials, for those drugs rather, all the materials have to go and be submitted to FDA 30 days prior to use. There's no requirement, however, that the company has to incorporate FDA's comments. It's not a pre-clearance or a pre-review provision. It's a pre-submission requirement.

One thing I have to add to that. The regulations allow for the voluntary submissions of

proposed launch materials. FDA encourages the submission of these materials, especially for drugs which have serious risks, such as for opioids. We encourage companies to submit the materials. We make it a high priority to get comments back to the company. We work very closely with the medical review divisions to do that. And our hope is to prevent misleading messages from first occurring.

DR. KIRSCH: Dr. Craig. Dr. Turk.

DR. MICHNA: I think they were referring to a question I had earlier. And this goes to Mr. Wolfe.

I'm a little confused by the chart that he presented and what the purpose of it was. To me, the scripts have been very consistent. There was a dip, but -- somebody could correct me if I'm wrong. But that was when Oxycontin went generic. And they lost to generic competition. It then became a branded product again, and there was no other generics.

So in looking at this, my impression is Oxycontin prescriptions have been consistent, if not a little lower. Sales are up probably because they raised the price. So I was a little confused of what

the purpose of the graph was.

DR. WOLFE: Well, it was just to show the Oxycontin, the brand name itself. I mentioned that before, in the data shown yesterday, the total number of oxycodone extended-release prescriptions for, I guess 2009, was maybe 7 or 8 million. So it is the majority now. I mean, I think that Oxycontin has become a brand name in a very unfortunate kind of way, and I think there's probably a lot of attraction to get back to more prescribing Oxycontin. The company has tripled its sales, tripled its prescriptions since the time that this criminal conviction occurred.

DR. MICHNA: Well, it really hasn't, only because it was a situational thing, where it was generic, and it went back to the branded product. So I don't think you can draw that conclusion now.

DR. WOLFE: The conclusion is simply that Oxycontin is selling more, the brand name Oxycontin.

DR. MICHNA: And I think the reason that there was an increase, and it hasn't been consistent -- look, I'm not a supporter of industry, but I don't want to mislead the facts here. The facts, I think,

reflect the fact that it went generic, and then it became a branded product again, not that there was an increase in marketing that produced an increase in sales.

I mean, I think we have to be clear when we present data, as to what it's actually saying. I don't want to mislead anybody here. And it seems like the scripts have been very consistent. And being a clinician, obviously, a product, whether it's been abused or not, there is a clinical need for it. And obviously, physicians with all the knowledge and all the issues with the misuse, still feel it's an effective drug for a consistent number of their patients, for whatever reason. That's all I'm saying.

DR. WOLFE: But just a quick response is that the "need" for probably more extended release is warranted by the situations that probably immediate release was created by this company. It's been sustained, if that's what you're saying. I think the company has done a good job sustaining the massive prescribing that they caused for a five-year period until they got caught by the FDA.

Yes. There's been a decrease because of some generic, but they are back in business again. It sold way more than they have paid in criminal penalties.

DR. MICHNA: Well, I think --

DR. KIRSCH: I think that we have data that was presented with two sides of understanding of what the data shows. And I think we could debate that for a long time, but we won't.

Dr. Denisco?

DR. DENISCO: Relative to promotional activities, in epidemiology, it's always difficult to find what causes what; what is the causality? What caused it and what is just merely associated? This is a situation where that case exists.

If we go back to the 1990s, certainly there were many calls by the WHO, by many pain societies, by individuals to relax the regulation of prescription opiates. However, if you look epidemiologically, the points of upturn in the morbidity and mortality data, it seems to be clearly related to sales of Oxycontin. And it's this whole problem, that is the number two

cause of accidental deaths, that seems to be able to be tracked back to the illegal promotion of this one medication, which had an effect of publicizing the desirability of prescription medications with front-page ads, front-page publications on both Time and Newsweek.

Because of the serious nature of this and the close relationship of this to marketing, I, number one, wonder if you have looked at the marketing data, and would agree with me, relative to the epidemiologic data. And number two, based on the fact that, prior to this, it was possible to get by with an immediate-acting opioid product or a very strong-acting product such as Dilaudid for a short period of time, until you can switch a patient over to a longer acting medication.

It seems with this high morbidity and mortality, that a program of protection, greater than what we have seen yesterday, would be warranted and would not unduly delay the treatment of patients to register somebody or for the physician to check a database. It does not appear to me that there was any

significant morbidity and mortality prior to the mid-1990s, when the problem, the morbidity/mortality problem, and the marketing of Oxycontin shot up.

There was no problem related to people getting medication immediately. And if it meant for a day or two, the nursing staff would have to run and get some more doses of medicine to administer to the patient until everything was clear. We did not hear any data that this was causing any problems, but we do hear data that the current situation is causing problems to the rate of second only to motor vehicle accidents.

Would you agree with that, based on your analysis of the promotional data?

MR. ABRAMS: A number of issues here. First, it is a complex issue. Part of your question is for practice of medicine, evolution of practice of medicine, or how it turns, and FDA obviously does regulate the practice of medicine.

Then, another part is for correlation of marketing data or sales data to the promotional efforts. And there's so many factors that go into the

sale and prescribing of prescription drugs, it's difficult. I have not seen anybody who's been able to tease out a promotional activity and have a direct correlation.

I think there's two main points here, as far as promotion. First, FDA's charged with ensuring that promotion of prescription drugs is not false, is not misleading, and is balanced, balanced with the serious toxicities, or risk which may be associated with the drug, as well as other material information, comments, and adverse events.

There's no limitation. FDA does not have any authority on the extensiveness of promotion. I often hear people saying, "Well, there should be a limit on how much a company can spend on promotion or how far it can do it." FDA does not have that authority. What we look at is the messages, whether they are accurate and balanced.

DR. DENISCO: Just quickly, that's where my point is exactly, that the initial messages, starting back from the 1990s, were not balanced. I don't care how much they choose to market. But the marketing was

false, and in some large way, contributed to the problem we're dealing with today, due to an unbalance of the advertisement, is my problem.

MR. ABRAMS: Just another comment on that. I think it's hard to correlate the promotion to what may have happened. But I think a more important point is, the agency has acted when it has seen misleading promotion. It has issued regulatory letters in the '90s. It has also issued a warning letter that Dr. Wolfe referenced in his comments. So when the agency does detect misleading promotion, we are prepared to act against it.

DR. KIRSCH: Dr. Flick.

DR. FLICK: Another questions regarding promotion. I just want to be clear.

Does FDA have the authority to require that this class of drugs marketing be cleared prior?

MR. ABRAMS: No, it does not.

DR. FLICK: Okay.

MR. ABRAMS: I may reference somebody from our legal department, if they want to add something to that.

DR. FLICK: Do you have authority to review, at some time, or require review of all the marketing materials?

MR. ABRAMS: We do not have the authority to pre-clear materials. We do have the authority, in certain cases, of Subpart E and H drugs, to require pre-submission. That would give us the opportunity to review the draft materials before use and then provide comments. We do not have the authority to require pre-clearance. That means approve. We do not approve actual promotional pieces before they go out in use.

DR. FLICK: But currently, this class of drugs, you do not require pre-submission of marketing materials?

MR. ABRAMS: That is correct.

DR. FLICK: Do you believe it should be the situation?

MR. ABRAMS: I would have to discuss that with other people in the agencies and respond later.

DR. KIRSCH: Okay. The next question is from Dr. Markman.

DR. MARKMAN: My question pertains to

several of the presentations from yesterday, regarding the so-called balloon effect. The balloon effect was referencing the -- related-to-access-to-care issue with regard to patients and prescribing of opioids.

It was sort of alleged or hypothesized that making education mandatory would, for physicians and prescribers and other clinicians, limit access to care. We heard in the public session today from two speakers, Dr. Katz and Mr. Porada, who have data to suggest that that's not the case, or that hypothesized balloon effect may be, in fact, imaginary.

So I was just interested in hearing from folks at the agency who presented yesterday, or any of the other presenters, any data to support the likelihood of that balloon effect occurring.

The reason I ask this is because, as a clinician in practice, who like workers in every other industry, I'm required virtually every month to take some sort of training test, whether it's to give conscious sedation or for infection control or to reduce my malpractice premiums, to show that I can safely make decisions and communicate with patients

and other colleagues. So it's virtually an ongoing process, to protect patient privacy.

So I just want to understand whether those things don't inhibit my ability to wash my hands or to give conscious sedation. In fact, they enhance my confidence that I can do it well. I invariably learn something, and it changes my practice.

So I just want to understand better, the evidence for a dampening effect on prescribing for the most prescribed drugs in America, if there's any evidence for that.

DR. RAPPAPORT: The access group went through this in quite a bit of detail, and looked at every submission from every stakeholder who had comments related to this, including data. I should say, when we asked for this a year and a half ago, we asked publicly for submission to the docket, of as much data as possible. We heard a lot of people say they had data. We got not a lot of data in the docket. We got a lot of opinions.

But based on the data in the docket and based on the opinions that were presented in the

docket and at the public hearings -- and that's all summarized in your background material -- the conclusion of the access working group and the overall REMS working group was that there could possibly be an effect that would be negative on access and that might cause the balloon effect to result in patients being treated with other drugs that might have worse outcomes.

Now, that's the conclusion based on the information we had. There may be additional data. And we do have, I believe, data from both Dr. Katz and Porada that has been looked at as well. So I think part of your charge today is going to be to assess the data that you have from us, that we summarized for you, and to consider whether additional data is needed, and then to make a decision about whether this is appropriate, that our conclusions are correct, or whether we need more information, or how to move forward.

DR. MARKMAN: That's helpful. Thank you.

DR. KIRSCH: So I'm going to go back to the list of individuals who raised their hands from

yesterday who we couldn't get to. I'd ask that the members of the committee, when I call on your name, if the question's already been answered, to pass.

I'd ask for the FDA, that maybe Dr. Rappaport could be the person who can assign the questions to the appropriate person, since many of the people from yesterday or some of the people from yesterday may not be here. And we'll do the best we can to answer the questions that the committee has. So the next question comes from Dr. Ballantyne.

DR. BALLANTYNE: I actually had a question from yesterday's presentation by the industry working group. And it was concerning, actually, Dr. Davis's presentation on education, particularly the education of prescribers. And the first item on the list, under education for prescribers, was, and I quote, "proper patient selection."

So I think that patient selection is such a critical issue. And in terms of the outcomes we've all been looking at, we seem to be focused on catastrophic outcomes. But in fact, there is another disastrous outcome, and that is failure to meet

treatment goals. I realize that we're not considering that so much here. But proper patient selection is critical to achieving the goal of a good outcome, in terms of pain treatment or improvement in quality of life.

My question really was, will this segment, in teaching prescribers through the REMS, be focused on how to select patients specifically for extended-release and long-acting opioids, or will it be in terms of selecting patients for opioids in general? Because I see that, actually, it could go both ways. It could be helpful, in that it helps us select the right patients for the treatment, or it could actually be unhelpful or negative, in that it encourages us, particularly if the drug companies are involved, in actually selecting people inappropriately for the treatment.

DR. KIRSCH: So there are a number of people in the front row over there from the industry working group, and I would ask if any of the individuals from that group would feel comfortable coming to the microphone to answer the question. And I'll remind

the individuals who come to the microphone to please introduce yourself prior to answering the question. Thank you.

DR. DAVIS: Eric Davis, with the IWG. And as far as the educational goals for the prescribers, this is one area where the IWG believes that we bring in third parties, the learned societies, those that are familiar with this topic and pain medications to assist us in forming the best training and educational program that we can. So the IWG doesn't propose any kind of training program on its own, but gets the material through the learned societies and the stakeholders.

DR. RAPPAPORT: Can I add something?

DR. KIRSCH: Please.

DR. RAPPAPORT: The choice of patient selections of the proper patient for opioid use is obviously a key component of how to properly prescribe these, and should be a key component of the educational program. And I agree that this is going to be written and created by the experts, not by anybody from industry, and not by us at FDA, just with

our oversight. And I want to remind you all that we will have the oversight to make sure that it's done right, and to not have it used until it is.

DR. BALLANTYNE: Thank you for that. It seems clear to practitioners that it is such a highly critical issue, and it's where we all struggle. I mean, I wouldn't even pretend we know how to select patients appropriately, but we certainly need to find out how to do that. And what concerns me is that it can only be done by our educational efforts outside this process, that this process cannot be unbiased, whereas what we do outside this process can, in terms of selection.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: Thank you. This question's for the FDA.

The REMS proposal is focused on the word -- I read the words education, voluntary, and encourage. And the question I have is, is education in this setting -- two questions. One is, is education in this setting the same as training, and is encourage the same as require?

DR. RAPPAPORT: We are requiring that education be for prescribers. Prescriber education is required. What we're not requiring is that they be tested for that and proven to show that they have reached a certain level of competence. But what we're doing is asking and requiring of the sponsors that they survey to make sure that a reasonable percentage of the prescriber population has been appropriately trained.

DR. DESHPANDE: As a follow-up, one of the proposed REMS does not include the mandatory patient education. And I was just going to make a comment based on two presentations we heard. I think it was Dr. Savage and Dr. Brason, that the loop for an effective solution, in their presentations, if I heard it right, included physician, pharmacist, and community or patient education as part of the total loop.

So I wanted to find out why, at the end of the day, this was left out of the recommendation.

DR. RAPPAPORT: I think when you look at the feasibility of requiring patients to be enrolled in

some kind of a program -- and you're talking about -- I think the number we estimated was around 4 million patients. And to capture that information in some kind of closed system that's going to guarantee that those patients have been enrolled, and therefore properly educated, that whole system appeared to us, and appeared to most of the stakeholders, which is what we based our decision on, to be so overwhelming to the public health system that it really was not feasible. And there are additional issues of stigmatizing patients and such.

Now again, we are open to hearing if people think we ought to step this up at this point, but we don't want to step out there with something that is so overwhelming to the public health system that it's going to collapse the whole process before we even test this out. It might be that we do have to go there eventually if what we proposed doesn't work.

DR. JENKINS: If I could add to that? Going back to Ms. Axelrad's presentation yesterday, let me remind you that our REMS authority is to regulate the sponsor of the application for the product. So

anything that we exercise has to be affected through the sponsor or the manufacturer of the product.

So some of the considerations that go into that type of a system is the feasibility and the desirability of having the sponsor in charge of those activities. So we did seriously look at the question of having every prescriber individually registered into an opioid REMS prescribing system, where they would be individually enrolled, tested, certified, and then they could prescribe the drug. We looked at having individual patients enrolled, so that they could be educated and certified that they could receive the drug. We also looked at having real-time verification of that prescriber training, patient enrollment at the pharmacy level.

Those types of systems do exist for certain products, like isotretinoin, where it's a much smaller scope of the number of prescribers and number of patients involved.

In the end, based on all the considerations you heard, we decided that that was not the direction we thought was appropriate for this program, keeping

in mind that one of the statutory requirements we have to meet is that it not be unduly burdensome on the healthcare delivery system and patient access to therapy.

So that's the judgment we made when we put this all together, and that's why we're putting forward the program that we are. You know we're interested in hearing your feedback on whether we didn't get that balance right.

We also were reluctant to create a registration system for prescribers of scheduled products when there already exists a registration system for prescribers of scheduled products. So if we created it through the REMS, the manufacturers of these products would have to create that registration system for prescribers.

We were concerned about whether that was the appropriate way to go when there is already a registration system. And as Dr. Rappaport said in his presentation, the more efficient pathway arguably would be to link it to the DEA registration. As you've heard, that's something that would require

legislation. We cannot do that under the REMS authority that Congress gave us under FDAAA.

DR. KIRSCH: Dr. Flick.

DR. FLICK: One thing that we have not discussed through these past hours is the cost. And I don't know whether cost is something that is under the committee's review. But I wonder what do we estimate the cost of this REMS program, and who will bear that cost. I see Dr. Neuman is here from Covidien. He might be able to give us some insight into what the REMS cost is for EXALGO.

DR. KIRSCH: Dr. Neuman.

DR. NEUMAN: Herbert Neuman with Covidien Pharmaceuticals. We don't split out the cost for EXALGO REMS by itself. We keep the cost for all of our risk management activities across our entire product portfolio. I can tell you our investments in that area are growing on a yearly basis, but for competitive reasons, I really can't get into our exact budget.

DR. FLICK: Thank you.

Dr. Rappaport, do you have a sense of what

this will add to the cost of caring for these patients and providing long-acting narcotics?

DR. RAPPAPORT: I don't, and I don't have a number in my head. But I can tell you it's going to be expensive any way we do this. Most of the cost will of course be borne by industry, but you know where that's going to get passed on to. And the more we do, the more cost.

And I'm not saying -- we don't take cost into consideration in making our public health decisions, but that is a reality that the more restrictive, the more costs there will be, because the expense of having registries and systems in place to monitor those registries would be quite high.

DR. FLICK: Thank you.

DR. KIRSCH: Dr. Woods.

DR. M. WOODS: Thank you. I'm not sure why you picked on me at this time.

DR. KIRSCH: I'm sorry. I got the wrong Woods. I'm sorry. I had the wrong Woods. If you have a question, you can ask it and I'll ask the other Dr. Wood after.

[Laughter.]

DR. J. WOODS: I'll be happy to make a comment, if you don't mind.

DR. KIRSCH: I'd love to hear it.

DR. J. WOODS: I want to go back to yesterday. It speaks a little bit to the issue of patient selection and how we can offer better care and prevent overdosed deaths. Tom McClellan told us yesterday that there were a couple of studies that suggested that overdose deaths occurred right after a script was written. They occurred if someone also had a script for benzo and if they had some history of overdose.

I'm wondering if we couldn't take the appropriate sponsors for those folks who have these scripts, ask them to stratify restrictions and agreements with their practitioners in ways that would help us prevent the specific problem associated with overdose, and actually design interventions, together with the sponsor, that would reduce the problem. In other words, deal very specifically with putting a patch on the hole.

In addition, this isn't in any way to speak against the more general issues that were discussed with the REMS, but it's something that I've been grappling with, in thinking that in some ways we're dealing with very general kinds of things that are dictated by the restrictions in ways that we have to move to satisfy laws, et cetera; at the same time, not dealing very specifically with the public health problem that's before us.

So that's what I was thinking about when you asked.

DR. KIRSCH: Thank you.

The other Dr. Woods?

DR. M. WOODS: Thanks. I have a couple of questions. The first, I don't know that will have an answer. But with respect to the epidemiology of the epidemic, so to speak, do we have any data to tell us to what extent the deaths and adverse events occur in the inpatient setting versus the outpatient setting?

DR. RAPPAPORT: Actually, folks from SAMHSA, do you have any -- No?

DR. KIRSCH: Please use the microphone and

please introduce yourself.

DR. DORMITZER: For deaths --

DR. KIRSCH: Please introduce yourself.

DR. DORMITZER: Okay. My name is Dr. Cathy Dormitzer. I'm an epidemiologist in the Division of Epidemiology in the Office of Surveillance in Epidemiology.

We did not present death data, but there is death data via the medical examiner data. And if it's in the medical examiner, those are deaths that are unattended. So they were outpatient deaths, not inpatient deaths.

DR. M. WOODS: Okay. I suspected we didn't have great data.

I have some questions related to the REMS program itself and how it might roll out. As I understand it, with the patient education materials, prescribers at the time of prescribing the medication, would provide patients with education material; correct?

DR. RAPPAPORT: Yes.

DR. M. WOODS: Then when the patient goes to

the pharmacy, they would again be provided that same material; correct?

DR. RAPPAPORT: At the pharmacy, they would get a Med guide, which would be similar but different.

DR. M. WOODS: Okay. When patients are admitted to the hospital, presumably stabilized on the medication, would it be required that the pharmacy at the time of admission provide them the Med guide?

DR. JENKINS: You're asking a very complex question. In general, the medication guide regulation was written for outpatient dispensing. And generally, they are not distributed in the inpatient setting. But there have been, I think, some exceptions where in fusion centers or other types of environments, medication guides have been distributed. But in general, no. They're not distributed in an inpatient hospital setting.

DR. M. WOODS: Thanks.

DR. KIRSCH: Dr. Terman.

DR. TERMAN: Frankly, I'm a little saddened by the last couple of days of discussion. Assuming that I get the education to treat my carefully

selected patients with exactly the right amount of pain medicine, I'm not sure how that is going to help get rid of abuse and misuse, diversion, addiction, and most of the deaths, according to the data.

When I talk to my opiate expert colleagues, like my realtor, she tells me that when she's scheduling an open house, the first thing she asks is whether people are on pain medicines so to avoid people participating in the open house, also going through medicine chests and finding things they're looking for.

So there's been some talk about storage and almost nothing about disposal. And so, most of the patients I prescribe opiates for have a long-term goal of getting off those opiates. I'd just like to know where we stand in terms of takeback or buyback programs to try and encourage people, when they do stop taking their medicines, to be able to get rid of their opiates in their security cabinets.

DR. THROCKMORTON: This is Dr. Throckmorton. Let me take a shot at that. It is a part of what we've been talking about in the last couple of days.

But you're right; we perhaps haven't focused on it as much as we could have.

It's part of a much larger initiative, that the FDA and several of the partners that spoke yesterday are working together on to try to make a difference. We are trying to minimize people keeping these drugs longer than they need to, minimize getting more of the drugs than they needed at the time.

How to affect that and how to use the REMS to make that more effective is one thing we'd like to hear your thoughts on. I would say, however, the other piece that we've talked about these last couple of days, is another aspect of it. The Safe Use Initiative that Karen Weiss spoke to yesterday is about groups working together to try to do this kind of thing more effectively. And at least, my own personal view is that that's much more likely to be effective than trying to use a program targeted like the REMS to achieve it by itself.

DR. JENKINS: This is John Jenkins. If I could also go back to some of my opening remarks yesterday in some of the context that the REMS fits

into? This is clearly a broad, societal problem with multifactorial causes that are involved in misuse, abuse, diversion, addiction to prescription opioids. We tried to make clear that we understand that the REMS cannot be the solution to all those multifactorial causes.

As I said in my opening remarks, our REMS is focused primarily at that doctor/patient interface, to try to help make sure that the doctors are selecting the correct patients, prescribing the right dose, educating the patients on safe use and appropriate use and disposal, et cetera, giving patient education.

We then see that there are kind of concentric circles of household contacts, neighborhood contacts, illegal activities that go beyond the scope of what we can really hope to achieve in the REMS. But we did notice in some of the data that approximately half of the product that ends up in the hands of people who are using it for non-medical purposes originated from that doctor/patient interface. Again, we regulate that area of this scope of problem, and that’s where we’re focusing our

attention.

Dr. Rappaport showed a slide at the end of one of his presentations yesterday that was a spectrum of parties involved in this issue. On the left-hand side was the prescriber, in the middle was the patient, and on the far right was labeled others, others meaning household contacts, neighborhood, illegal activities, the whole scope of others. And if you go back and look at that slide, the REMS banner was over the prescriber, and the safe-use banner was over on the right side for the others.

So it has to be a multifactorial intervention. So we're not under any presumption that the REMS program will solve all of those problems. It's just really focused on trying to make sure that doctors are prescribing appropriately, educating patients appropriately, and patients are behaving appropriately in how they use the drug and how they store it and don't share it.

That's where we're trying to intervene. Will it solve the entire problem? No. Hopefully, it will have some impact as part of a multifactorial

program under safe use, with the other partners, with DEA, to focus on the illegal activities. So just keep that context in mind as you're thinking about the proposal.

DR. KIRSCH: Dr. Craig. Dr. Todd. Dr. Carter.

DR. CARTER: I just wanted to agree with some of the comments that were made by Dr. Woods and Dr. Terman, that I'm quite concerned that we haven't, up to this point, identified any unique risks that are associated with this class of extended-release drugs; that is risks that are neither outcomes, like death, or risks that differentiate this class from the immediate-release opioids. And I think until we have those risks identified, it will be very difficult to implement mitigation strategies that can address these very specific risks, particularly in light of the fact that we've seen data thus far that the prescriptions for the extended-release compounds have been increasing, and increasing at a faster rate, and that the problems, per number of prescriptions for this class, are greater than those for the immediate-

release drugs.

So I think, until we identify the unique risks that are pertinent to this class, it'll be difficult to generate these specific mitigation strategies to address those risks.

DR. KIRSCH: Dr. Kosten.

DR. KOSTEN: Thank you. Perhaps, some of these are summary points rather than addressed to specific people who have testified. But the things that are striking to me as we're talking about voluntary training or voluntary -- not even training -- voluntary education, when the pharmaceutical industry has plenty of data to indicate how worthless that is as influencing physician behavior. And that academic detailing, in many ways of making and influencing physician behavior, are very well known to the pharmaceutical industry and very well utilized, yet, all of that's being avoided, as far as I can tell, in any of this discussion, of what the pharmaceutical industry could actually contribute to this.

The second concern that I have is that

implementing best practices in medicine has, in fact, a very strong set of principles involved in implementation science. The Veteran's Administration has, in fact, done quite a bit in this over the last 10 years. And yet, I hear very little about how the FDA's going to make any use of that expertise in implementing a program or a project, that the aspects of which are very well articulated, in a system that's been in place for a long time, including things that have been mentioned by several of the presenters that didn't represent the pharmaceutical industry.

The third thing is that we should be targeting bad prescribers, and that seems to be an issue that the DEA could be of great help to us. And while I did hear some discussion of putting the advisory group of the various federal agencies back together again -- I think that was from Dr. Schnoll -- I don't see anything in these documents that suggest these kind of interagency collaborations are going to occur, or that in fact the state registries of who may be your problematic providers are going to be utilized in any way.

Then finally, as, again, several people have said, I see no distinction between the immediate-release and the extended-release types of opiates. And at least, in Texas right now, the biggest problem that we have with an opiate is an immediate-release one, Vicodin. It is making millions of dollars for several hundred physicians in the state, who don't seem to be pursued by the criminal justice system. And I find that despicable. I think the cooperation level between the agencies seems to be outrageously uncoordinated.

So I think there are very serious issues there, but I'm quite concerned that we're not dealing with them.

DR. KIRSCH: Thank you.

Dr. Covington?

DR. COVINGTON: Thank you. I think I'd most like to express a concern. You know, we're relying here on voluntary education, and it's hard for me to come up with a scenario in which we can have an authoritative answer as to exactly what education we're going to be providing.

We've heard that people taking over 100 milligrams a day of morphine equivalence are more likely to die. I think Dr. Ballantyne showed that there was essentially no evidence supporting use of over 195 milligrams of morphine a day in chronic use for non-malignant pain.

Our background materials tell us that the typical dose is 300 milligrams of oral morphine a day, and all of our experts who give us lectures tell us that there's no ceiling. We're being told, too, that there's hazard associated with combining opioids and benzodiazepines because of increased death. And yet we have literature showing that benzodiazepine use is actually a predictor for chronic opioid therapy.

We're told about the special hazards of prescribing opioids to people who have a pre-existing addictive co-morbidity. And yet the insurance data from the Pacific Northwest tells us convincingly that an addictive disorder predicts, number one, a likelihood of an opioid prescription, number two, that it's likely to be a Schedule II, number three, that it's likely to be in high doses.

So we really have a huge amount of sort of discrepancy in what people believe about opioids, based largely on the fact that we have very poor data and lots of biases with different ones of us, in terms of which answer we would think is correct.

Finally, it seems to me, in some of my forensic work from years gone by, is that the people who are doing the most egregious practice were the ones who thought they were best educated about opioid pharmacology. So that raises a question as to whether anything voluntary is going to be useful.

So I guess the two questions, is how can we come up with something authoritative in an area where there's so much ambiguity? And number two is, is voluntary physician education really going to do the job? Thank you.

DR. RAPPAPORT: I'll respond to that. Now, you know what we face pretty much every day. There isn't a lot of clear-cut data out there. And there are a lot of very strong opinions from some very well meaning, and some very highly educated and experienced people, many of whom are in the room today.

So when we have this type of a situation, this is exactly when we need to come to an advisory committee meeting and have an appropriate mix of the experts, sit around the table and discuss this information, and make some recommendations.

I think we did a pretty good job this time in pulling together a group of you who have a broad expanse of experience in pain management, in addictionology, in the interface between the two, and in related safety issues.

So that's why you're here today. And the second question you asked is one of the ones we're putting to you.

DR. JENKINS: If I could just add to that, we've heard some discussion about the voluntary nature of the prescriber training on the individual prescriber. Keep in mind, what we're proposing is that the sponsors will be required to make the training programs available to the individual prescribers. They will be FDA approved for content, and then they will be expected to meet certain performance goals for demonstrating that prescribers

have, in fact, completed the training and that there's evidence that we're hopefully seeing some increase in the awareness of the appropriate prescribing practices.

We're hoping that there will be take-up of this through CME programs. That's why we had those speakers here yesterday. We've also heard from partners at the federal and state medical boards, the CME that's related to the REMS could be required for licensure in individual states.

So we're looking for ways to leverage that voluntary training for prescribers to become not so voluntary, but not directly through the REMS program. We've heard from the Federation of State Medical Boards that their members might actually require that physicians take the training and have evidence that they've completed it in order to maintain their license.

So it is voluntary on the individual prescriber. It's mandatory for the sponsors to make that training available. And they will have performance goals under the REMS to meet, to show that

prescribers are in fact taking the training. We're looking for incentives through CME. And we're hoping to partner through safe use with other stakeholders, who can help us nudge that training out of the voluntary space and into the required space.

Keep in mind, the only way that we could require an individual prescriber to be trained would be to have some way to keep track of every individual prescriber and check off that they have in fact completed the training. That means that you have to enroll every prescriber into the program, and you've heard why we considered that and in the end, decided not to go there.

You may tell us that that's a way you think we should go. But that's trying to help understand voluntary for the individual, mandatory for the sponsors. And we're hoping to leverage through partners and other activities to make the voluntary individual training not so voluntary.

DR. COVINGTON: May I follow up on that point?

DR. KIRSCH: Yes.

DR. COVINGTON: So I think one of the potential pitfalls with the voluntary training or education is that if we can agree that participating in such education is a responsible activity, and if we can agree that prescribers exist along a spectrum of responsibility, then I think that it's likely that those that are least responsible will participate in the education and the training.

So even if you can show that a high proportion of prescribers are participating in education and training, I think the individuals or who those people are in the proportion that are not participating will be critically important. And I think this is a significant concern with regard to voluntary training and education.

DR. KIRSCH: The FDA has given us lots of material to discuss in our questions. But before we discuss them, I turn the floor over to Dr. Rappaport to charge the committee in our discussion of these questions.

DR. RAPPAPORT: Thank you.

Okay. So you've heard about the problem of

prescription opioid abuse and misuse, not just here today, yesterday, but you've all heard about it for a long time from many different sources, including your own work. And you've heard about the benefits of these products and how important maintaining access to them is to many patients in this country. You've heard from a lot of experts and from a variety of speakers at the open public hearing today, who had a variety of opinions about where our proposed REMS is right and where it isn't right.

Given the goals of reducing addiction, overdose, and death, I think we can probably all agree on those, but we would like to hear if you think that we shouldn't be trying to reduce those or if there are other goals that we should be focusing on. But given those goals, and the goals of maintaining access and not overburdening the healthcare system -- again, recall that those are mandated by the statute. And given the feasibility -- and you need to keep this in mind as well -- of implementing a REMS that will cover over 700,000 prescribers and somewhere around 4 million patients, we're now going to ask you to

discuss a number of issues, beginning with your thoughts and concerns regarding this proposed REMS.

Then, after some general discussion, you'll be asked to vote on whether you agree with our proposed REMS or not. Following that, whatever way the vote goes, we're going to continue the discussion and ask you to discuss, even if you voted against having this particular REMS, how best to implement the educational components of a REMS. And finally, how to measure the impact of a REMS on both abuse and misuse, as well as access.

This is, granted, a daunting charge to you. But it is really essential that we and the public hear clearly from you, because that's the point of calling you together day. As I said a little earlier, in response to Dr. Covington's comments, there are no easy answers. If there were data out here that was clear cut, we probably wouldn't need to have you giving us input; we would be able to make a decision clearly.

So without that, we need your expertise and your experience to help us. Whether we're on the

right track or not is going to be what we would like to hear from you. And if we're not on the right path, we need to hear from you how we should modify the path that we're on. And I want to thank you in advance for what's going to be quite an effort today.

DR. KIRSCH: So I'm going to read the questions, and then we're going to discuss the questions. And then, I'll do my best to summarize the discussion for the FDA. And when I do my summary, please correct me if I'm misrepresenting the group opinion. As I look at the list of the 36 members of this committee that we have, I'm a little bit concerned about getting a consensus opinion, but we'll do our best.

So the first question is, please discuss the problem of misuse and abuse of the extended-release and long-acting opioid analgesics and its impact on public health. We're going to start a new list.

Dr. Wolfe?

DR. WOLFE: I'm going to refer back to Dr. Denisco's remarks because it's right on the point. There's been a change in culture over the last 15

years or so, certainly led by Purdue and other companies have followed, to shift a larger proportion of opiate prescribing to extended release from immediate release.

So I think that part of the problem of misuse and abuse has to do with this ratio shifting. I mean, the data that were in the briefing package were very clear, measured by DAWN, emergency room visits or almost anything else, that the dangers of the extended release far swamp out the immediate release.

So if the overall endpoint of the goal is to reduce the amount of abuse, et cetera, et cetera, an intermediate step to that would be changing this ratio. So I think that the problem as evidenced by the harm is clear, differential between what we're discussing, because we're not discussing changing immediate release; we're talking about what can be done about the extended release.

I think that the problem is there, and the impact on the public health is much more over time than it used to be, and the over-time than it used to

be is largely related to the increased use and percentage of opiates that, even though it's the minority of use, the rate of growth, as a couple of people have alluded to, is enormous. In direct proportion to that, we are seeing more deaths, more emergency room visits, and so forth.

So I think it's a well-documented problem, and I think that we need to expand from the list of REMS as to how to take care of it.

DR. RAPPAPORT: Can I just make a comment? It would be helpful, since what Dr. Wolfe just said is that there's a clear-cut more serious outcome seen with these long-acting, extended-release products. And some other people have said that, and yet there are a number of people around the table who have said there's no difference in the seriousness of the consequences of the immediate release, and that they should be included.

That's an important question for us, is to how broad this REMS should be. So I hope there will be some discussion between the two opposing thoughts on this.

DR. KIRSCH: Dr. Markman.

DR. MARKMAN: Would you prefer that we wait to speak to Dr. Rappaport's direct question here?

DR. KIRSCH: No.

DR. MARKMAN: Okay. So with regard to the question of the public health problem and the issue of balance here, balance between access and safety, access to care and public health safety with regard to these medications, I think from what we've heard, we're not currently in balance. We're out of balance. That's the status quo.

When these medications that we're talking about are contributing to the most common cause of accidental death in 10 states, and a number of which will likely increase and we maintain the status quo, I would argue that the current state is not one of balance.

Equally important as a practitioner, I feel that we currently operate -- and someone who prescribes these medications, that we operate in an environment of voluntary education for the most part with regard to these medications. And what's being

proposed is a continuation of voluntary education. And I don't think that that will change the status quo, which is unacceptable.

DR. KIRSCH: Dr. Farrar.

DR. FARRAR: With regards to the very specific point about extended versus immediate release, from my perspective, the issue revolves around dose. What makes extended release more dangerous is that if you chew it, you get an acute dose of up to 80 milligrams of Oxycontin, or now with the long-acting hydromorphone, et cetera. And so I think the issue, from my perspective, is that concern.

Clearly, if the REMS is imposed in whatever form for extended release only, it will reduce the amount of extended-release use, and I would expect a concomitant increase in the use of the short acting.

There's a second issue, which is that over the course of years, there's been a very strong push to try and get dosing to be given less often. There's excellent evidence that dosing that's given less often increases compliance. That's important for your blood pressure medicine. That's important for your

antibiotic. I have no evidence specifically, but I would be willing to bet that most of the people around the table agree with the fact that there's no problem with compliance with pain medications.

In fact, if you're going to give something that doesn't work, give it frequently because it works better. As a neurologist, I call that the placebo effect. But in opioid use, there's been a push to try and get the long acting to be taken. And there's concern, physiologic concern, again no clinical data, that long acting may induce more level tolerance, and that in fact, short acting might actually be better for many kinds of pain. We don't have data, however, on that, adequate to know that.

My concern in limiting this to the long acting is that I think that the short acting has an equally potentially dangerous problem, and I would actually strongly encourage including both of those in the REMS program.

That said, we have to start somewhere. And in the interests of trying to move this all forward, I would hate to have it all get stalled for years based

on that discussion, and would be very much in favor of moving ahead with the implementation for long acting, assuming that long acting is a measure or is some sort of a way of getting at at least some of the population who use the drugs acutely.

So my argument basically would be summed this way. I would hope that in fact, these programs would cover all of the opioids, long and short acting, but that in terms of the requirements for things, those could be imposed for the long acting as a place to start, with the clearly intended goal of extending them once we had more data.

DR. KIRSCH: Dr. Boyer.

DR. BOYER: I feel that it would be incorrect to omit immediate-release products from a REMS. I think that it should be included. You're correct. I can kill you just as dead with an immediate-release product as I can with an extended-release product. If there's a perception that they're safer products, it may be because deaths are coded a different way. It's difficult. Every medical examiner discussion I've heard is that it's difficult

to code an oxycodone product as being from one formulation or another in determining a cause of death.

I think they're also coded a different way. People who die of immediate-release products may die of respiratory depression, but they are also at risk for dying from fulminant hepatic failure. And that's sometimes lethal, if it's not caught in time, or if it's not treated properly. But I'm not convinced, given the low value of the data surrounding the whole milieu of opioid-related fatality, that anybody can say with confidence one group is safer than another; one group should be eliminated on that data.

DR. KIRSCH: Dr. Beardsley.

DR. BEARDSLEY: I also am concerned about not including the immediate-release product under this REMS for much the same reasons that have been iterated already. But also, another consideration is that if we don't include the immediate-release REMS under this current REMS, we'll be back next year or in two years, discussing a special REMS for the immediate-release products. These REMS are just going to proliferate

and eventually become a very onerous burden on the healthcare system.

So I think we should really consider including at least the immediate-release product under this current REMS to prevent that sort of imposition on the healthcare system in the future.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: Thank you. I wanted to echo similar concerns raised with not including the immediate release. And the point I'd like to make is that, in addition to the dosing considerations, et cetera, I think it's confusing to patients and the public to make a distinction between it's the form and it's not the active.

So it's the same therapeutic agent, same pharmacological properties, and it's a somewhat artificial distinction in how it's actually being dosed. And considering that I'm not a pain specialist, but I would expect that it's a natural progression for a patient with chronic pain to maybe have started out with the immediate release and perhaps progressed to extended release over time for

reasons of convenience and pain management, et cetera.

So I think it creates an artificial, suddenly you now get the extended-release product and you have this education, whereas there was none of that type of education at the point of starting opioids in general. I can appreciate the logistical challenges of doing this on a broad scale. And I would agree with Dr. Farrar, it's better to get started with something as opposed to arguing it.

But I think if you go with just extended-release and long-acting, then there really needs to be very careful thought of how you communicate the why we're doing it there, and not leaving the unintended implication that the other forms are better, and that's why they're not having the same amount of risk management.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: I think, just as a practical matter, we know that the extended-release products are where we think we're seeing the most problems. And immediate release may well be involved in that, but clearly, the overwhelming problem is due to extended

release.

Historically, it was thought that extended-release products would be safer and have less addiction. However, that has not been borne out to be the case. I did not see any slides yesterday that showed that they are more effective. So what we're left with is a medication that's not more effective, and is of higher risk. But nonetheless, it is where the higher risk is, and we should sort of get started somewhere.

The problem with any of these is that I think good people are going to do the right thing, good patients, good doctors. And if the gentleman from the DEA is here, I'd love a comment. Nothing that we've seen is going to address the proliferation of pain clinics in south Florida. And this is on CNN. This is on any of the local news channels down there. The DEA said we had a closed system, so they know where every pill is. If that's the case, then they should know the huge number of pills that are being dispensed out of a clinic, which is very unusual.

They showed pictures in the bathrooms of

Oxycontin, with the comments, "Ask for it by name." If you go to CNN, or maybe it's on YouTube or whatever, or just, "pain clinics south Florida," in Google, you'll see this, and it's just an unbelievable thing.

These are the problems. This is where I wish the REMS would attack. We don't want to make it more difficult for well-meaning patients and well-meaning doctors to make it a pain in the neck. I would think we would want to make it difficult for the doctors who are running these kind of pain clinics -- I hate to even call them that -- and the poor patients who have become ensnared in an addiction, due to these very unscrupulous and I would say immoral doctors. That's what I would like to see a REMS do.

Just a brief comment to the FDA council. I have truly nothing -- I did not mean any implication or any negative comment to the FDA. I have nothing but the utmost respect. But as was said, the laws are such that it must be a reactive situation. It's very difficult to be proactive. And to be proactive would mean the FDA would need to know a problem's going to

exist, and then try to react to it, which would require a crystal ball. So that's just unrealistic. But there's nothing but the activities.

The same goes with Purdue. The people who were in charge of Purdue back in the criminal days are not the same people that are there now. But nonetheless, the consequences that the actions of those people have wrought is still bothering us and killing people and causing a great deal of human suffering.

We talk about morbidity and mortality, but I have to put a plug in for the horrible life-destroying events around a case of addictive disorder, and how many families have been destroyed, and how many people have gone to prison and lost all kinds of things.

DR. KIRSCH: I think we need to go onto the next person.

DR. DENISCO: Okay.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: I've got a couple comments. The question to the committee on number 1 is it a public health problem? My answer is yes. And I agree

with the other members of the committee that wanted to include the immediate release because this is an issue for the class of opiates.

My concern for the extended -release and long-acting group in particular is that of dose, as somebody mentioned before, particularly for the pediatric patient. One pill will kill you, or can kill you, depending on the size and the metabolism of the patient. So if we're starting somewhere, then this is a good place to start.

The second part of this for me is that we heard yesterday from Dr. Bickel the response about the SES and ethnicity in this problem, that there are specific populations that are at even higher risk for the problem. And as the REMS is being clarified, I want to make sure that those issues are addressed so that we don't have something that feels good but doesn't do good.

So finally, I think it's necessary but not sufficient to address the total problem, and it may be the first step, as Dr. Farrar said.

DR. KIRSCH: Dr. Rappaport?

DR. RAPPAPORT: Yes. I just want to put one thing on the table so everybody's aware of it. I think it's part of this conversation. We've already taken the first step with the REMS that we've been working on for the oral transmucosal fentanyl products, which are considerably more restrictive and have registries for patients and for prescribers.

DR. KIRSCH: Dr. Berger?

DR. BERGER: Actually, I have a few things. I, like some others at the table, like Dr. Terman, have actually been quite sad these two days, being a pain and palliative care doctor. I mean, when this was just put up, I'm like, okay, well, that's kind of nice. But with this REMS, how is REMS and education going to help this huge public health issue?

Nobody believes more that pain education needs to be done, because physicians know nothing about pain management. I mean, absolutely nothing. And physicians know nothing about opiates. That, I would absolutely agree. But we have a huge public health issue. But in this whole discussion, I'm still very unclear in the epidemiology, like how many

patients have died, and how many are those who are people who have taken drugs because they got them off the street or from family members or not patients who have taken the drugs illicitly. I'm not clear from these two days what that number is.

With those people, we need to then figure out if educating the physicians is really going to make the difference. And I'm not sure that's going to make the difference. We then need to figure out what kind of steps need to be taken to stop that problem, which I think is going to be more than one or two steps.

We then need to address some of John's issues about safe storage of the drugs and things like that; the transmucosal fentanyl issue that Bob, you just raised, and that was one of the things I had thought about. Having been involved in many of those studies early on, I don't know that much about addiction. But it seems to me, that's not something in these two days that we've heard about being a huge problem in the addiction world.

So is that because of access; is it because

of dosage; was it because of the lockboxes; is it because of the education?

Should we maybe retrospectively look at why has that drug not been a problem? And just even from an FDA point of view, can we learn something from that experience, and what can we learn from that experience? I don't know, but is it worth maybe looking at what has been done from that drug, because that seems to be less of a problem than the Oxycontin. Why is that so different?

If training is going to be about opiates, I think it's going to be a problem. You know, the patient that came up spoke beautifully about, "I went there not only to get opiates, but I went to have my pain treated." And pain management is more than just opiates. So if you're going to teach us about opiates, and not about psycho-, social, spiritual issues, and about complimentary modalities, and everything else about pain management, the physician's not going to know what to do.

So if you're just going to teach about extended-release opiates, you're really not going to

get very far. And so, maybe we can discuss this in the afternoon when you discuss educational methods and what you want to learn about what you want us to talk about.

The other thing that I thought was something -- the other presentation that was discussed that I thought was very intriguing, and maybe should be raised, was by Mr. Brown, Carlton Brown from ONS, where he mentioned that maybe a pilot REMS should be introduced. Rather than bringing this huge REMS program out and saying this is what it is, bringing out some pilot, and looking at an evidence based, and starting to pilot something. Looking at some evidence based, rather than bringing out something big and not knowing exactly what we're doing might be something that we want to do.

DR. KIRSCH: Many of the comments that have been made by the last several members of the committee really have revolved around the issue of REMS and not really pinpointed the issue or question at hand. So I'm going to take the chair prerogative and try to summarize what I understand the committee is saying

about the question at hand, and then, move on to the next question, because I think that will address many of the issues related to REMS that had been appropriately discussed.

So, for the specific question about please discuss the problems of misuse and abuse of the extended-release and long-acting opioid analgesics and its impact on public health, I believe the consensus of the opinion of the committee is that our country has a huge problem right now with abuse and misuse of the extended-release and long-acting opioid analgesics, and it has a huge impact on public health in the United States.

I think there's a good consensus on that. I think there's less consensus about the effect or the role of the immediate-acting analgesics, opiate analgesics. And I think there's a real concern about the immediate-acting analgesics, but not the same level of concern as there is for the extended-release and long-acting drugs.

If I misrepresented what the consensus of the committee is, please provide me with some

feedback.

Dr. Kerns.

DR. KERNS: I hope this speaks to the point. I like the way this was phrased, putting the focus on impact on public health. I think a key message that I've learned from my public health colleagues is something about message bringing, and the simpler, more direct and sustainable the message -- less complex messages are important.

I think, therefore, from public health, in trying to do something at a public health level, two things I would make. One is, it's about opiates. Don't exclude or try to be specific about extended release, long acting versus the opioid class more generally. And the other is that within the context of REMS, I hear a lot about targeting prescribers, pharmacists, and then, patients. But I don't hear a lot about an expenditure of resources at the level of a public health campaign. And I would like to see the REMS initiative, if it's possible, within the scope of the legislation, to I guess, encourage or require industry partners to engage in an ambitious public

health campaign to address this issue.

DR. KIRSCH: So to restate my summary, I think the wording is important. So the consensus of the committee is that the use and misuse and abuse of opiates is a huge public health problem for our country. We believe, however, that the largest concern exists with the extended-release and long-acting drugs.

No? Okay. I'll make it more strong based on the feedback of the committee.

We believe, as a committee, that there is a very significant problem with misuse and abuse of opiates in the United States, both extended-release/long-acting and immediate-acting opiates. And this problem has a huge impact on public health.

Dr. Krantz.

DR. KRANTZ: I agree. But I really think that the thought behind the FDA, to sort of target in on long acting, is a real important one, because I think, although we've heard from the Office of Epidemiology, that there's a linear relationship between the amount of opioid put into the market by

us, the prescribers, and the number of deaths.

I think there is some example of disproportionate levels of death, despite the prescriptive use. I think we've seen the data from the DAWN, where clearly, you had a relatively higher risk associated with the long-acting opioids – specifically, Oxycontin.

As an addiction physician back in a prior life, there is one specific medicine -- I think industry got it right. We want to be sure we have enough focus on methadone as its own unique pharmacologic agent. In Utah, if I recall, there's about a 500 percent increase in the prescription, yet about a 1,500 percent increase in the deaths. So there is something unique, and I think Doug certainly knows about methadone's properties. It's got complex PK in terms of PD. I think PD can cause arrhythmia.

So I'm not saying that we have to eliminate the short acting, but I think starting with the long acting is a very prudent first step.

DR. KIRSCH: So I think FDA has heard the concerns of individual members of the committee.

Based on the feedback that I got from my summary, we'll stay with that summary and ask the FDA to also take into consideration of the individual views that have been expressed.

The second question is to please discuss the goals of the proposed REMS, the appropriateness of the REMS components to address the misuse and abuse of extended-release and long-acting opioid analgesics, and the potential burden of the proposed REMS on the healthcare system, and patient access to these analgesics.

Based on the consensus of opinion on question one, I'd ask the FDA that we restate the question and make it apply to all opioid analgesics because the committee feels that there's significant risk for both groups of analgesics.

So that being the question, I'll open it up to further discussion.

Dr. Gray.

DR. GRAY: I guess I'm somewhat cynical that volunteer training is going to make much of an impact. As others have said, the biggest problem in Tennessee

are the prescribers, the mercenaries that are willing to write these scripts. And if they can't find them in Tennessee, there actually is a shuttle that goes from northeast Tennessee down to Broward County twice a week. It costs $40 round trip and the bus is full every time they leave.

My guess is that the doctors in Broward County will not take the course. If they do, they'll continue business as usual. So really, to make an impact on this, somehow, we have got to deal with the dishonest providers that are willing to write these prescriptions. These doctors are sometimes referred to me by the Board of Medical Examiners. And they say, "Well, they need to go to a prescribing course." And I say, "They don't need a prescribing course. They know a lot about writing prescriptions. What they need is a course in ethics or a conscience. And unfortunately, they don't have a conscience. I can't give them a conscience."

DR. KIRSCH: Thank you.

Dr. Vaida.

DR. VAIDA: I'd just like to start off by

saying one question I wanted to ask yesterday and didn't get the opportunity was we didn't see any error data presented. And I think that what would have just at least been interesting hearing some of the questions, especially with today, how many deaths and what is it from.

There's a lot of information out there, depending on how big you want the numbers, where people have died from inappropriate prescribing. I mean, people have received fentanyl patches post-dental. They've received fentanyl patches. They've left them at home and their kids got them. There's a lot of preventable information out there on the use of opioids, both long acting and short acting.

So I think, with that in mind, I'd just like to make a few comments on this question, and just say that there is that information out there, too, that I think we should remember that it does exist. And we may not need big numbers when we're talking about preventable. So when we look at inappropriate, I know we're breaking out inappropriate and misuse. But many of us in the safety field put those together, just as

the IOM had those together back in '99, misuse included errors and preventable.

Prescriber education. I believe we do need that. It's on the inpatient and outpatient side. There is more than enough information that we have. There's a big inpatient issue with the use of opioids, and a lot of it is misprescribing these drugs. So although my colleagues here from ASHP had said that it may not be needed, I think it's certainly needed. And it should be across the board.

With the mandatory, I think heard from FDA is that, yes, I mean, you make it mandatory for license renewal. And I think you had the players here in the room yesterday that will put that into place. I mean, this happened years ago with when I had to renew my license. And HIV was big, and all of a sudden, it became that I needed X amount of credits in that. So it became mandatory, and I think that is something that you have the people in the room to help with that.

Another thing is that I think that hearing on the abuse side -- and again, I don't think how deep

we could get into that -- and hearing from the FDA, saying that part of these elements of safe use includes the drug may be dispensed only in certain healthcare settings. And we've seen that with some restrictive programs. I think you should strongly consider that a prescriber can't dispense Schedule II narcotics.

I mean, what that would take, how that would be put into place -- would that solve the Florida problem? Now, I don't know if it would solve that, but the majority of those are actually being dispensed by the prescriber. And this is a Class II narcotic, and you need a safety net.

Now, would you have pharmacists out there dispensing these things? Maybe. But you do need that safety net, which I'll just talk about in a minute. And I don't think the burden is yet a question. I don't think any of this is a big burden that you'd put on because everyone needs CME to get license renewal. I think the important thing is – and not to jump ahead -- is that it's specific. It does have to talk about pharmacology of these drugs, pharmacokinetics, and it

does have to talk about how to educate patients, and be specific from what we heard today, too, on storage and disposal and having a safe or like real specific items.

Same thing does with pharmacist's education. I believe that it should go beyond that, that pharmacists do need education, once again, inpatient and outpatient, because the errors we get, we wonder how were those drugs dispensed. So I think pharmacists do need the education in this. And once again, it is something that should be through license, that there should be so many credits for license renewal. That includes medication safety, and it includes safe use of opiates. Once again, very specific.

Another thing I think you should seriously consider is mandatory patient counseling at the outpatient pharmacies. I mean, I think this is something we've seen. Several states have it. The state of Arizona has mandatory counseling for all new prescriptions. And I'm not talking about the CMS, the over counseling where you could sign off. This is

every patient that gets a new prescription -- we've done observation studies -- get counseling, and the pharmacists take it seriously.

The burden? I'm not sure what the burden is. But I'll tell you, every large chain that has a store in Arizona does it. They may not do it in Texas, but they found a way to do it in Arizona.

So I think this is an opportunity here of, once again, pharmacists acting as that safety net, through prescriber education, pharmacists education, and also mandatory counseling for opioid prescriptions. We consider this a high-alert drug. And that means, when it's misused, when it's improperly used, it could cause more harm than any other drug. And you know, we don't have a lot in those categories, but I think that's something that's very important.

Then finally, with the abuse, I think that the Safe Use Initiative is something that the FDA should look for the partners, push that out, and also, look toward the industry to help support some of that as part of the public service, although it'd be driven

by the FDA. Sorry for going on so long.

DR. KIRSCH: Thank you.

Dr. Farrar.

DR. FARRAR: I think this is a tremendously complex issue, and I would ask my fellow committee members to try and keep separate some of the issues we're trying to address. We've heard about Broward County. And frankly, Broward County needs to be addressed by the law. We've heard about accidental overdose by people taking too much because they didn't understand it. That can be addressed by patient education. We've heard about getting it from your friends, stealing it from your mother or your colleague or from a friend that you have. That might be addressed by lockboxes.

It seems to me that the devil really is in the details, and if we talk broadly about sort of this and that and the other thing, without keeping it clear what we're trying to prevent, it's going to be very confusing.

In terms of the specifics, they're asking this question. Clearly, there is going to be some

cost to doing this, and who ends up bearing that cost is going to be somewhat controversial. It seems to me, though, that, in fact, as was suggested by Dr. Ballantyne and others, good training about pain care with a focus on helping to prevent the accidental overdose and abuse, but with the initial piece of it being good pain care, could actually improve pain care as an outcome of this project, as opposed to reducing the use because of the ways it's imposed.

Clearly, the devil again being in the details. It needs to be checked. There needs to be data collected. And there are ways to do that without imposing significant costs, and I'll address those when we get to the next question. But it seems clear to me that if it is done wrong, there will be significant costs, and it will limit the amount of care, perhaps, in a way that would be detrimental.

If it's done in a way that makes sense, which is appropriate education, I think with a requirement, although how that's implemented I think needs to be discussed --if there's appropriate education for physicians, for patients, and for the

public, that it could in fact benefit the overall care of patients with pain.

DR. KIRSCH: Thank you.

Dr. Flick.

DR. FLICK: We're being asked to address question 2, discuss goals. I think the goals, as I understand them here, are to improve the appropriateness of prescribing this class of medications. I think the REMS, as the FDA has written it, is appropriate in that.

However, as proposed, I think the REMS is unlikely to have a significant impact on that goal. And as to the third portion of that question, the burden, I think that there is certainly some burden. As Dr. Rappaport described, there will be a significant amount of expense associated with this.

I'm not sure whether the results that will be achieved through this can justify that burden. However, I do recognize that this is an incremental process, and that we should proceed down that incremental pathway toward something that at some point is likely to have a positive impact on the

public health.

DR. KIRSCH: Thank you.

Dr. Michna.

DR. MICHNA: What I wanted to discuss was in the proposal, should this voluntary system fail, then there was words to the effect that a mandatory system connected to your DEA.

Based on what's been said by Dr. Jenkins and others, in terms of your working with the boards of medicine, and more to the point of my colleague next to me, I could understand at the beginning why tying it to the DEA would have been an easier way of going, given if we were under the pressure of doing that. But if indeed we're going to have an interim period where we're going to have voluntary, why not then propose that should it fail, then we will go to a broader education system tied to your medical license with the boards of medicine?

I think a more global approach to education is important, even for those that don't prescribe, which was what was stated yesterday, that even if you're not prescribing these, you're still going to be

affected by the patients with this in your practices.

So my question is, basically, is the FDA rethinking that part of it, and would they consider, if this fails, to consider a more broader approach tied to your medical license, and eliminate all the potentials for the opt-outs, the secondary unintended consequences that have been discussed.

DR. JENKINS: This is John Jenkins. I'll try to address some of that.

We have to operate within the authority that Congress gives us through the laws, so we don't have authority over licensing physicians for practicing medicine. We don't run the DEA registration system for prescribing controlled substances.

What we were referring to is if this program were not to be successful, and we wanted to go to a more required-type of a program for training or whatever, that would be under the REMS program. So we would be executing that through the manufacturers. So our ability to escalate this would be to require the manufacturers to build those registries that individual prescribers would have to be enrolled,

trained, certified, and patients would have to be enrolled, trained, whatever, like was done for isotretinoin. That's the authority that Congress has given us to operate under.

As we said, we acknowledge -- and I think it's probably in our reports -- that a more efficient approach might be to, if you wanted to go that direction, link it to the existing DEA registration. DEA registration requires that you have a valid medical license but doesn't require any specific training beyond that in prescribing controlled substances.

Essentially, as it was described yesterday, you demonstrate that you have a license, you fill out the form, and you pay your fee, and you get your registration number. It's really a tracking system, more than it is a system designed to try to oversee the appropriateness of the prescribing in that sense.

So that's what we were referring to. If this doesn't work, this incremental approach doesn't work, then our authority would allow us to work through the manufacturers, the sponsors of the

applications, to build that parallel system. And we were very concerned about the burden of that parallel system. But also, we heard a lot of feedback from patients and other stakeholders about, do we really want to have the manufacturers of these products be the ones who are in charge of that system to register prescribers and patients?

But to answer your question, that would be how we would escalate the REMS, would be through the sponsors having greater requirements to develop these systems. Any linkage to the DEA registration system is something that would require legislation through Congress, not something we can do under our authority.

DR. KIRSCH: Thank you.

Dr. Hatsukami.

DR. HATSUKAMI: I too was a little bit skeptical in terms of the effectiveness of a voluntary approach. And I'm not really sure what would be the best mechanism, whether it be the DEA registration or working with other stakeholders like the state medical licensing boards to actually get to a point where it would be more mandatory.

But I think what we also need to take a look at, carefully, too, is the nature of education that will be provided to the prescribers. Dr. Gallagher had said yesterday that what doesn't work are the CME lectures, seminars, and readings. And so the FDA certainly needs to pay careful attention to how that education will be provided to the prescribers. It appears that more of an interactive approach might be effective, and perhaps, using an online interactive, innovative educational approach should be considered.

The other issue is whether -- I'm not really clear, based on research, since the research seems to be limited, whether the education that is provided, whether it be innovative or not, whether that's going to translate to actual change in behavior in the physicians' prescription methods or the way in how they inform their patients.

So, I think we need to really carefully maybe do some pilot testing or something prior to implementing the REMS to assure that there is some kind of translation of their education into actual alteration in behavior.

DR. KIRSCH: Dr. Porter.

DR. PORTER: My comment goes back a little bit in the conversation to several speakers. And I think that Dr. Farrar and Dr. Flick caught the essence of what I wanted to say, that we were addressing the potential burden of the proposed REMS on the healthcare system. And then, clearly, somehow, it's going to trickle down to the insurance companies, to the patients themselves. But perhaps the committee could address what the relative benefits are to that system as far as saving dollars to the healthcare system and dropping addictive programs, and that those kinds of things might be something we should consider when we go down to the metrics; something that would be included as far as the success of the program goes.

DR. KIRSCH: Thank you.

Dr. Wolfe.

DR. WOLFE: I'm concerned about time lost by having voluntary education, particularly in the hands of the company. I realize and agree fully that that's within the limits of FDA's authority. And when I asked Dr. Rappaport yesterday, he gave a predictable

and correct answer; they cannot support legislation unless it's been cleared.

But I think we could take a stand that would cause this to happen sooner rather than later, to have this involved with DEA. DEA is the logical. That's not to say that state medical boards couldn't also get involved. But it would seem to me that such a large national problem with an already existing controlled substance act created agency, the DEA, that we should discuss as part of this question what can be done now, as opposed to saying, well, if this voluntary doesn't work. I mean, voluntary generally doesn't work for almost anything having to do with health. So I would just put forth that.

In terms of the burden on the healthcare system or access part of this question, I agree with Dr. Denisco. I don't think the access question has to do with the ratio of extended release to instant or immediate release. I think that people would still have access, who need them, to opiates, that a larger proportion of people than are now using the IR form would be using it if we retrained people. So I wanted

to introduce the phrase "retraining people" because a lot of people have gotten untrained and detrained from appropriately using IR to using ER because of all the campaigns.

So just to summarize, two things. I think we should discuss, maybe not under this question, the idea of recommending from this panel that the process of starting to move towards legislation that would empower DEA to add this to what they have to do. And secondly, I think the access question is contrived in the sense that if you're saying someone would not have any access to opiates, that would be a big problem. And I don't think that's where we're dealing here. It's the relative and inappropriate proportion of people that are getting ER opioids.

DR. KIRSCH: Dr. Turk.

DR. TURK: In addressing the question, the first part that we're presented with, please discuss the goals of the proposed, I think if the goals are to reduce morbidity and mortality associated with opioid prescribing, I don't think anyone could disagree, and Mom and apple pie would be about the statement. So I

think we would all agree that, yes, the goals are commendable.

I think it's important that we realize, and I think Dr. Farrar mentioned this, alluded to this, that we're talking about at least two, maybe three, different populations here. We're talking about trying to prevent inappropriate prescribing by unscrupulous providers. And I don't think anything in the REMS or any REMS we could come up with is going to do that. So we're not going to be able to eliminate problems.

Can we reduce the problems? Then we're talking about the prescribers who might benefit from greater information, education and for patients who get greater information. And the patients who get the greater information would potentially trickle down to the potential family members and other people getting access to their medication.

So I think that if we keep those two apart, contrary to -- I think Dr. Vaida said something about lumping them together. I think we really need to keep those two things separate, and I think we drift when

we start trying to solve everything, by looking at these as being one group.

Then, if we look at the comments that we've received from some of the people from the FDA, it's that we hope, we may, they may, they might do better, or they might be incentivized by CMEs. That, for some reason, doesn't give me a great deal of comfort that that, in fact, is going to be the case. I think it was Dr. Katz who mentioned that he was here eight and a half years ago when REMS were first begun to be talked about. We've had many attempts along the way. There are huge numbers of educational programs, and we see the numbers are getting worse.

So I don't think that the REMS, as being presented, is likely to have a huge benefit. It's definitely not going to affect the unscrupulous providers. It might have some marginal benefit -- I don't think a huge benefit -- on the current, "good prescribers" and the patients that are there.

I think that the discussion we've had repeatedly about voluntary versus mandatory, I think that discussion is something we really have to come

back to. I think, in the past, voluntary efforts have not done very well. Voluntary efforts in the area of opioids have not done very well. It is not for lack of CMEs being available.

DR. KIRSCH: I'm going to ask one other person to speak, and then I'm going to try to summarize the comments so that we can, after the summary, after we agree on the summary, have lunch and come back for the vote.

Dr. Brull.

DR. BRULL: Thank you. I'll try to stay on focus and be short. I, too, agree that the REMS are -- the goals are very good. But I don't know that we know the potential impact is known yet. We don't have any data. So I'm in somewhat of a dilemma, because on one hand, REMS is a reasonable first step to increase patient safety, but since we don't have any data, we may not want to pass anything. But not doing anything is also not reasonable. So I think that even though the REMS may not be sufficient at this point, I think it's a reasonable first step.

Back to the first question, I don't know

that the two statements or the dichotomy was necessarily that the two things were mutually exclusive. I think we can say that the problem is for all opiates, whether they're immediate or extended release. But at this point, we opted to, or the FDA opted to, focus on the extended release.

There are two other points. I don't know that we know the decay of knowledge of the REMS. And I think that this is something that we may want to advise on starting a demonstration project. I mean, how often do we have to do this? Will a single REMS be sufficient? How often do you repeat it?

Finally, I think that we need a realistic assessment of the time that's required for prescribers and patients. Again, we don't think that it's going to have much of an impact. But I don't know that we have hard data to base our judgment on this. So before we continue to pile on additional time requirements, I think that we should actually see whether it's realistic or not, especially as healthcare changes are underway.

DR. KIRSCH: Okay. I'm going to try to

summarize the opinion of the committee. You guys don't make it easy. So I think we will all agree that the goals of the proposed REMS are laudatory. They're certainly appropriate. However, it's unclear whether the REMS components are adequate, particularly in their voluntary nature to address the issue of misuse and abuse of extended and long-acting analgesics.

The potential burden of the REMS, although it may be significant, must be balanced by the potential benefit of the REMS, both in human health as well as in savings and expense in other areas of the healthcare system. And that's my assessment of what I heard.

Any corrections or additions to what I've said?

Yes, Dr. Vaida?

DR. VAIDA: I think that summed it up. I think the only comment, at least that I'd make, is the last part with the burden. I really didn't feel that I heard a lot of people say the elements we're talking about would be a big burden right now. And I don't know if that's just me, but I mean there would be a

big burden in cost or whatever. Probably the only thing is with the DEA. So I don't know if we should soften that to just say that going forward it may not be as big a burden as we think. I just throw that out.

DR. KIRSCH: Well, I think what we heard yesterday and what we heard a little bit about from industry today is that there is going to be a significant financial burden in implementing this REMS program. It will cost a lot of money; however, the education and training and determination of competency occurs, that will cost a significant amount of money. So I think tempering that cost with improvement in human health and savings in other programs might be necessary because of the current abuse problem that we have. I think that sends the same message.

Dr. Farrar.

DR. FARRAR: The FDA cannot ask us to recommend, or about the recommendations, that we try and encourage the U.S. government to move towards a more cohesive approach to this problem. And I'd like to just echo what Dr. Wolfe said and actually ask the

committee whether adding to the summary would be that we would strongly encourage the collaboration between FDA and other groups within the government, and that this committee recommends that some of that collaboration and cooperation be written into law.

The FDA cannot do anything with that, but I think it would be an important step in trying to handle some of these issues. I don't know if it's an appropriate motion, but it seems to me that -- I certainly feel strongly that putting a little bit of teeth into this thing would be a good idea, and I don't know how best to do that. But certainly, I think we should encourage that that step be taken.

DR. KIRSCH: I think it's appropriate, and, certainly by the comments I've heard the committee make, that the committee strongly encourages the FDA to collaborate in moving forward on this project with the other important governmental agencies.

Ms. Krivacic.

MS. KRIVACIC: With regard to the burden question, I think one of the things -- and maybe this follows onto what Dr. Farrar is talking about, is we

haven't really understood the cost benefit of this. And that's what it speaks to, is there hasn't been a cost-benefit analysis put in place.

Perhaps, the FDA working with various other agencies or even some outside foundations to look into that, some type of cost-benefit analysis as it relates to implementing a REMS, whichever REMS we decide on.

DR. KIRSCH: Dr. Kerns.

DR. KERNS: Yes. Building on Dr. Farrar's comment, I agree and would further extend that to -- I think he was mentioning legislative action where it's needed. And also, I really am impressed, in this entire meeting at the call for more science. And although the REMS plan calls for evaluation, I think it's incumbent on FDA to call on its partners in NIH, VA, other funding, research funding agencies to establish this or call for this topic to be a priority for science.

DR. KIRSCH: Dr. Nelson.

DR. NELSON: Given that this drug amounts to the second most frequent cause of preventable death, it sounds like in this country, I think the threshold

to consider something to be unduly burdensome is fairly high. And I would suggest that it does depend a little bit on which patient population or which professional practitioner or whatnot you're talking about. The need to protect the patients, the public, and particularly the children and teenagers who are really involved in a lot of these issues, I think is striking, and the threshold should be fairly high.

DR. KIRSCH: Dr. Flick.

DR. FLICK: I wonder if we could ask the Chair to specifically address Dr. Farrar's point after the vote and after lunch. I think my sense is that there are many members of this committee who believe that the REMS approach is, as defined by the FDA, too narrow a focus on a very broad problem that needs to be addressed from a variety of directions. And I think it's important for us as a committee to express that sense and have that sense reflected in the minutes of this committee, so that the FDA may use those comments. So I think it's important we address that at some length but not at this point.

DR. KIRSCH: I would agree. And maybe it

would be appropriate for Dr. Rappaport or legal counsel for FDA to come back after lunch and maybe remind the committee what's within the realm of your abilities or authority in the FDA. I know it's been talked about on several occasions, but it keeps on coming up, so we can discuss it more extensively.

DR. FLICK: Dr. Kirsch, if I may, I wonder if the question that we could pose right now is would it be helpful to the agency for this committee to express its views as to the breadth and depth of the problem and the approach.

DR. KIRSCH: Will the FDA comment?

DR. JENKINS: I think this discussion is very useful, not only for us, but also for the other observers of this process. We ourselves cannot change the law to have DEA-linked educational training if that's what you feel is needed. So this is a public advisory committee meeting. If you feel that's the way the law should be changed, then you're free to state that.

Hearing that from you is useful for us, but I think there are other stakeholders and listeners who

can hear that as well. So if that's the way you want, take a poll and get some advice, I think that's fine.

DR. KIRSCH: Thank you.

Dr. Kosten.

DR. KOSTEN: Thank you. I certainly agree that it's hard to imagine how you could make this overly burdensome on providers, considering the damage that's being done. But I really do think -- I've heard this several times and I'm not sure it's sinking in much -- to roll out a national program with no pilot programs, with no data back, with essentially blind, is just absurd. There needs to be pilot programs. They need to have a timeline, perhaps of a year or so, to see how they work. There are multiple very good ideas here.

There's also programs that exist already. Buprenorphine had a rollout, had a mandatory training, had a DEA cooperation. There's legislation behind it. There are things that are in the laws already. There are examples. I don't see quite evidence of that showing up in this. And yet, the models are there. There's a whole other set of -- again, I regret to say

this, but in spite of being abused by the VA for many years, the VA does have examples. They've used it, it's been effective, and there have been evaluations, and implementation science is a science, and there's data on how you implement things.

I am just struck by, as I said, pilots, pilots, pilots. I mean, why are we sitting still? Thank you.

DR. KIRSCH: Dr. Jenkins.

DR. JENKINS: I heard some calls from the committee that you wanted to hear more from our regulatory experts and legal experts on authority. Ms. Axelrad is here and can't be here after lunch. So I just wanted to let you know, if you'd like for her to address that point, now would be a good time.

DR. KIRSCH: Ms. Axelrad, could you provide us with a summary of what your authority is and where your authority does not extend so we can discuss it afterwards?

MS. AXELRAD: Yes, I can do it, yes, very briefly.

Basically, as Dr. Jenkins indicated, our

authority runs to the regulated party, which is the sponsor who holds the application for the approved drugs. And our authority under the statute is that we can require the sponsor to implement a REMS when we determine that a REMS is necessary to ensure the benefits of the drug outweigh the risks.

Once we make that finding, in accordance with the statutory criteria that I described yesterday, then we would send a letter or letters to the sponsors, asking them to implement a REMS program. They would submit a program. We would review it and approve it.

I think that the issue of pilot programs is somewhat complicated, given the way the statute is written, because it doesn't say that we have authority to require any kind of a pilot program. And once we make the finding that a REMS is necessary to ensure the benefit of the drug outweigh the risks, I think it would be difficult to justify only trying something out in one place and not having it apply to all the drugs that are out there. It would be difficult to justify that under the statutory standard.

So one of the things that we've talked about, we in our discussions have also talked about pilot programs. And there have been a number of programs in various states and across the country where things have been tried. And I think that looking closely at those data to see what has worked and what hasn't worked might be the best thing that we can do in terms of a pilot program.

I would also say that, as I've said, the REMS, all REMS, have to have a timetable for assessment in them. And if we initiate some parts of a REMS program, or a REMS program such as the one that we've proposed, we will be assessing it on a regular basis. And to the extent that we're able to develop meaningful metrics that would allow us to see how well that program is working, it can function, in a way, as a pilot program because it can be broadened or extended or made tighter, depending on the results of that assessment.

DR. KIRSCH: So further questions for Ms. Axelrad before she goes?

Dr. Farrar.

DR. FARRAR: The statement I made before is that the buprenorphine situation might lend an example. And I wonder if you could help us to clarify that, because in fact, a special license is required for that. That's in some ways what we're talking about, thinking about, with opioids. And if you could compare that, that would help us to understand it.

MS. AXELRAD: Yes. I am not an expert. Bob, or perhaps one of the people in the division can speak directly to the details of the buprenorphine program. But we have looked at it as a model, and we have talked to various people about what has worked and what has not worked about that program.

DR. JENKINS: I think the most important distinction is that was specific legislation. That was the Drug Abuse Treatment Act of 2000 that specifically allowed for that outpatient treatment of patients with drug dependence, but it also set up the procedures that required DEA to establish a separate registration number and required that people seeking that registration number had to have a certain amount of training. I think it's eight hours of training.

So it's specific legislation for that situation. That's the biggest distinction, I think, between that and a REMS.

Taking it to the next step, there's been conversation about linking this training, that you think is needed for opioid prescribing, to DEA registration. That analogy is why we keep saying it would require specific legislation to require that prescribers who want a DEA registration number would have to demonstrate training and competence in opioid prescribing.

DR. KIRSCH: So I'm going to hold further conversation, as it is time for lunch and ask the FDA whether the summary that's been provided is clear enough, with the addition of the last comment, which is that in addition to the committee urging the FDA to work with the other appropriate agencies, as a public statement, as I know it's not within the purview of the FDA, but we believe that appropriate legislation should be generated in order to protect patients who are being prescribed these dangerous medications.

Last comment. Dr. Deshpande?

DR. DESHPANDE: I like your summary with one exception. I think what I've heard is that the word "burden" is different from the word "cost" in a lot of our minds, so that if we said that, yes, there may be additional or substantial cost, the summary may more reflect what I heard, which is different from the impression that the word "burden" gives.

DR. KIRSCH: Okay. We'll change the word "burden" to "cost," still being offset by the potential benefit of improving the human health, as well as improving the cost or decreasing cost in other areas of healthcare.

With that, we're going to break for lunch. We'll come back from lunch at 1:15.

(Whereupon, at 12:16 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

DR. KIRSCH: Committee members, I'd ask if you take your seats, we're going to have a vote. Okay. I assume that the vote will be electronic.

Has the FDA staff prepared the electronic system for the electronic vote?

I'll read the question. Please vote on whether you agree with the agency's proposed REMS for extended-release and long-acting opioid analgesics and discuss the rationale for your vote.

So, for those of you on the committee who have not voted previously on this committee, let me interpret the question as I understand it and tell you how the vote's going to work.

So the interpretation of the question is if you vote yes, that means that you agree with the content of the proposal that the FDA put forward yesterday on the details of what the REMS would include. If you vote no, that does not mean that you disagree with the idea of REMS in general, but just that you're disagreeing with the details of the REMS as is currently proposed by the FDA.

What will happen is they'll get the electronic system working. You'll vote yes or no, or abstain. After everyone has voted, they'll put a list up on the screen that has all of our names with how we voted, yes, no, or abstain. And then we'll go around the table one by one and explain why you voted how you voted.

So for example, if you vote no, and said, "I believe that a REMS program is important, but I don't agree with this detail or that detail," that's your opportunity to explain how you voted.

Anybody from the FDA want to clarify what I said or disagree with what I just said?

DR. JENKINS: No. I think we agree with that framework.

DR. KIRSCH: Okay. And is the FDA staff -- I don't see anything flashing here.

Is the electronic system working?

Dr. Todd?

DR. TODD: Yes. Just one question. So this will be the only vote we take today; is that correct?

DR. KIRSCH: Yes.

DR. TODD: Thank you.

DR. KIRSCH: Any other questions about the vote?

Yes, Dr. Wolfe?

DR. WOLFE: Since it is written in a sort of absolute way, I am interpreting it to say you need to agree with everything in the REMS in order to vote yes.

DR. KIRSCH: That's my understanding as well.

DR. WOLFE: Everything? Right. Okay.

DR. KIRSCH: Everything in the proposed REMS that was presented by Dr. Rappaport yesterday.

For the FDA staff, are you ready for us to vote?

So again, everyone must vote. We won't be able to see the results of the vote until everyone pushes yes, no, or abstain. FDA will tell us when everybody has voted.

DR. KOSTEN: Is there any way for us to know that it's registered?

DR. KIRSCH: If it's not, FDA will tell us

as it was said.

TECHNICIAN: You can feel free to press the button more than once.

DR. KIRSCH: The last button that you push will be your vote.

[Voting.]

Has everybody voted?

TECHNICIAN: We're still missing one vote.

DR. KIRSCH: So everyone push their vote again, please.

[Voting.]

DR. KIRSCH: Okay. So for the record, voting yes was 10; voting no is 25; abstain is zero. And here are the details of who voted yes and no.

So we will start with Dr. Bickel. The idea is to express why you voted like you did. And if your sentiments have already been expressed by someone else, you can say, I have nothing to add.

DR. BICKEL: I voted no because I didn't think that the REMS, as proposed, was adequate to produce change in the nature of the problem. I'm concerned about the approach of sort we know that

there are some bad actors. We know that there are particular patient populations that are particularly susceptible to the adverse consequences, but what we're going to do is one size fits all instead of trying to identify the nature of the problem and specifically gear the solution to that problem. And to me, that seems to be both a waste of effort and energy, and wrong focus of our attention.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: Yes. I voted no. The reason is much the same as my colleague, and also that, essentially, this will be an expensive project. And whether we call it expensive or a burden, it's going to be a very resource-consuming project. And that is eventually going to be borne, not by a system of health, but rather by the patients. One way or another, it will be borne 100 percent by the patient. And I feel that this is not going to make any significant effect and is really just window dressing.

DR. KIRSCH: So if you could clarify for the record, is it that you don't believe a REMS program at all would be appropriate or that a different type of

REMS program would be most appropriate?

DR. DENISCO: I'm sorry I wasn't clear. I do believe a REMS program would be appropriate, but not this program, because it's not dealing with the specific problems sufficiently.

DR. KIRSCH: Dr. Krantz?

DR. KRANTZ: Yes. I voted no. I would first acknowledge Bob Rappaport and his team. I thought they did a really good job sort of balancing a very complex and nuanced issue that we're facing. But I guess overall I felt like the data, that education, communication plans, medication guides are effective in mitigating serious risks is almost nil, to copy Denisco's point.

I think, in this sense, "we have to match," as Thomas Jefferson said, "the hole with a commensurate patch," to use -- I think, Dr. Gallagher gave that lecture on day one. And really, when you look at 14,000 people dying on an annual basis, that's more than we've lost in Iraq and Afghanistan since 2001 in active duty. This is a big public health concern.

So I really think that the components of the REMS need to be stronger, including elements of safe use that are a little bit more declarative and restrictive. So again, I support the REMS in spirit, but I think it has to have a little bit more of a robust implementation plan.

DR. KIRSCH: Dr. Markman?

DR. MARKMAN: I concur with Dr. Krantz's statement. And again, I would like to acknowledge the agency's outreach, which I thought was excellent throughout the process. But the implementation and the follow-up, and the educational requirements, I think need to be more robust as a first step.

DR. KIRSCH: Dr. Gray.

DR. GRAY: I also voted no for the reasons already stated. I'd also like to see the immediate release included.

DR. KIRSCH: Dr. Ballantyne.

DR. BALLANTYNE: Yes. I voted no, and I also concur with the previous statements. My particular reasons for voting no were that I think that the process should include the immediate-release

opioids as well as the extended release. And I also have concerns about the educational piece in particular, which I feel should be more confined to risk management and not so much how we manage pain, or particularly, how we use opioids for pain. I think that belongs in a different process.

DR. KIRSCH: Dr. Boyer.

DR. BOYER: I voted no. I believe a REMS program is appropriate, but I don't think this is appropriate in scope.

DR. KIRSCH: Dr. Kosten.

DR. KOSTEN: I voted no. I agree with all the reasons that were given, in spite of running up against a congressional opposition or whatever, or takes an act of Congress, I still think a pilot study or two would be worth doing, and using some of the examples, for example, buprenorphine. And I also thought that leaving out an audit and feedback-type of mechanism that targets individual providers is very weak. And as one of the other speakers, one of the guests said, this needs to be a training program, not an educational program, and it has to be mandated.

DR. KIRSCH: Dr. Berger.

DR. BERGER: I voted no; agree with all the other speakers. I think we also need to understand how much of this is patients versus those not prescribed the medications. I think this is a huge public health problem in terms of abuse, but I'm not sure how much of this is the non-patient problem, especially coming from the palliative care approach.

I strongly believe that this needs to start with a little bit more of an evidence base, and we should start with demonstration pilot projects to get a little bit more of an evidence base, and understand what we're doing.

DR. KIRSCH: Dr. Mark Woods.

DR. M. WOODS: I voted yes. And I believe that the program as proposed was a good start. While it certainly was not perfect, I think we've seen lots of evidence that we have an epidemic.

I also want to respond to one of the things that I've heard that I think I have a little bit different opinion on, than others in the committee. While I understand that there's interest on the part

of other committee members to include the immediate-release products, I'm supportive of first focusing on the extended-release, long-acting products because, number one, they are novel drug delivery systems; and number two, they contain much higher amounts of drug per individual dosage units. Because of those two unique features, I think they probably do deserve some extra attention and education.

So while I understood people wanted to include the immediate-release products, I think the complexity of those dosage forms maybe deserves extra attention.

DR. KIRSCH: Dr. Terman.

DR. TERMAN: I voted yes. I agree with the FDA Scope working group, that this public health problem is not just about long-acting opiates, despite the fact that that is all the current REMS plan addresses. Nonetheless, any successful teaching of the patient assessment, drug safety, and careful follow-up for physicians prescribing long-acting opiates will generally also apply to immediate-release, short-acting opiates.

Further, such teaching will remind prescribers that opiates are only one tool in appropriate pain management, and that opiates, sadly, can be part of the problem, rather than always part of the solution. Ideally, this prescriber training would be mandatory. But I have come to the belief that the FDA, by itself, cannot implement such mandatory training. And as we've seen, this problem of opiate abuse and misuse cannot simply wait, without action, until appropriate databases are constructed or coordinated.

Federal agencies, such as the DEA or NIH, come alongside the FDA in this effort, or researchers get funding for conducting published studies on appropriate metrics for this problem. REMS are legislatively mandated to be dynamic, and this is a start.

Sadly, the real start needed is not as easy as training prescribers to use opiates appropriately, if that's easy. Somehow we must convince the public, including each of us and those we love, that opiates -- and prescription drugs for that matter, for the most

part -- are not the cure for their problems, but evils frequently necessary to help mask symptoms, and should never be shared, hoarded or kept unsecured anymore than we would allow access to our explosives.

DR. KIRSCH: Thank you.

Dr. Brull.

DR. BRULL: Thank you. My heart said yes; my head said no. So I guess I'm heartless; I voted no. Although I strongly support the idea of REMS, I think that the qualifier was, do you agree with everything that was proposed. And I think that that was imbalanced and what made me vote no, although I do fully agree with the idea of a REMS.

I don't think that it addresses some important issues of prescriber training, which should be mandatory, public education about safe storage and disposal, cost, and evidence of the effects. So I do think that we need pilot studies. Thank you.

DR. KIRSCH: Dr. Hatsukami.

DR. HATSUKAMI: Yes. I voted no. And although I do believe that a REMS is appropriate, I don't think that there was sufficient evidence to

convince me that the program that was proposed would have a significant impact on public health. And I also thought that we should include the immediate-release formulations.

DR. KIRSCH: Dr. Carter.

DR. CARTER: I voted no as well. I agree that a REMS is a good idea in this case. I voted no on the basis of I felt that there was inadequate identification of specific risks to the opioid class in general and the subset of opioids that we refer to as the extended-release or the long-acting opioids, risks that lead to the outcomes such as addiction and death, and also, on the basis of the seemingly ineffective and voluntary educational and training strategies.

DR. KIRSCH: Ms. Krivacic.

MS. KRIVACIC: I voted no. And while I don’t dispute the seriousness of the risks associated with opioids, I want to commend the FDA on acting quickly to want to put something in place. And especially, I do agree that a REMS is necessary.

However, I do believe that we need to be

very cautious and deliberate when we move forward in trying to implement something, especially something of this large a scale. Dealing with a public health crisis is the way I would describe this, especially since as Americans, that 80 percent of the consumers of opioids are Americans. So this is really a key problem that we have.

I do believe in rolling out something like this. We have to understand the underlying causes, and that way we can put in place effective approaches to dealing with this and in the end have successful outcomes. And so I also agree a pilot program is warranted.

DR. KIRSCH: Dr. Covington.

DR. COVINGTON: I voted yes, which I think in part represents a triumph of hope over evidence. I mean, I think the REMS as proposed is severely flawed. I agree with all the people who voted no in that regard. On the other hand, I think we not only have an epidemic of drug abuse. It comes at the end of what everybody acknowledges was an epidemic of misinformation. And I think one way to correct an

epidemic of misinformation is to create our own epidemic of better information.

I have hope that we can put together a group of scholars who can come up with, if not reasonable guidelines, at least reasonable -- you know, this is the likelihood your patient will die if you do X. And I think that sort of information will ultimately, potentially be transformative to some extent, and it's a start.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: Yes. I voted no. And I mentioned before, I wish there was some little bit more strength in it. But I'll just take the approach of what would have made me vote yes. And I would have voted yes if it extended beyond just extended release and if it included pharmacists' education.

DR. KIRSCH: Dr. Michna.

DR. MICHNA: I voted yes. This is a huge problem. And, unfortunately, I don't think it's one that the FDA or these type of regulations are going to resolve.

That being said, I think when you balance

all the things that could have been against all the things that it is, I think this was a fairly balanced rational first step in this whole area.

Do I think the REMS as proposed is going to have the impact that's expected? No. But we're missing data on so many areas of this whole problem, that I think it would be, in my estimation, a good first attempt.

DR. KIRSCH: Dr. Kerns.

DR. KERNS: I voted no. With due respect to my colleagues in the FDA, I felt that the presentation and the proposal fell far short in terms of meeting an acceptable first step. So I disagree with my colleagues who voted yes. I thought that the plan could be much more clearly informed by the science that we do have and data that could more specifically inform even the first steps in a plan, as articulated by the FDA.

I thought that it needed to include immediate-release products. I was not compelled by data that would argue otherwise. I thought that the plan should more specifically articulate a step-wise

approach to an ultimate goal of mandating training, not education. And then, in that context, the step that was proposed, related to education, could be appropriate, but it needed to be placed in that broader, step-wise plan.

I thought they needed to or could expand and explicate the evaluation plans, and more clearly and specifically, speak to issues about plans for incorporating implementation science, and a step-wise approach to implementation, as well as just simply an articulation of the goals or the endpoints for evaluation.

Then, I was particularly disappointed with the scope of or the explication of the public health campaign. I view this as a serious, most serious public health problem, and I think that the efforts should be equally distributed, in terms of development of a plan, targeting providers, consumers, and the public more broadly.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: Elaine Morrato, and I voted yes. And I just want to echo what some others have

said. I commend the FDA for exercising their expanded authority under FDAAA to help address this public health problem; it's very critical. And I commend them for the tremendous effort to obtain the extensive stakeholders' input and feedback, and their thoughtful, transparent consideration of that feedback.

I ultimately voted yes because I believe we cannot not act, and it's a reasonable place to start. Educational training will be the foundation of any REMS, and we should get going on doing that, and doing it with consistency and with excellence. And I also appreciated the perspective that the agency shared regarding the practicality and feasibility of executing a REMS within the FDAAA legislation that they're working with and appreciated that the REMS is just a component of a much needed and important safe-use initiative and other stakeholder.

Now ultimately, I would agree, though, with the other colleagues that I would endorse ultimately mandatory physician education. I believe it's very important, as was mentioned, that there's ultimately

very strict performance guidelines such that if the voluntary is not working, that it quickly rolls over into mandatory. I would also ultimately like to see that it's targeting both immediate release as well as extended release and long acting. And I had the same concerns as many committee members, in terms of the sufficiency of the education.

I just wanted to add a couple comments because I wasn't able to during the discussion section, because the way I interpreted the proposal from FDA is we do have some flexibility in detailing what exactly is education. So I would echo Dr. Kerns' comments and suggest that we really reframe and elevate education to a scale of a multifaceted and integrated promotional public health campaign.

So I agree with the FDA's concept of having an approved core content. As we heard from DDMAC, this is a departure from traditional educational promotional oversight, so I think this is a very good thing, that we have consistency in message. However, what we heard from both the agency and the industry working group is that I'm very worried that the way

education is being currently framed, it's not sufficiently funded, nor will it be conducted with state-of-the-art training and promotional methods that are required for maximal effectiveness to actually change behavior.

I think we should tackle this the same way that you tackle commercial marketing. We should market the drug safety behavior with the same degree of sophistication, scale, and timeliness that's done in the commercial sector.

What does that mean? That means that we put in the investment to do the formative research, that we understand accepted physician and patient beliefs, the norms, intent, and behaviors before you design; that you pilot test the materials; that this all gets built in as part of the development; that you give careful consideration to prescriber and patient market segmentation, and the different educational messages are tailored accordingly, whether that's by specialty, clinic setting, or social economic characteristics; that we actually think about not just listing features of what's safe use in a Med guide, but we actually

think about this, is how do you translate these features into ultimate end-user benefits that would be such to motivate someone to actually change their behavior; and that the FDA really require that there's careful thought, just like you do with a promotional advertising plan, what is the reach, what's the frequency of the message, what is the media mix of the message, are we doing it of sufficiency in terms of shared voice relative to promotional activities, that there's sufficient share of voice in safety; and that, ultimately, it's imperative that there's a timetable.

I believe there's a unique public health opportunity here for the FDA to set the bar high on what world-class safety education can and should be. And often we say time is money in a private sector. I believe in the public health sector, time is people's lives, and we should get on with it and not have another seven years of debating the need for this.

DR. KIRSCH: So I voted no. And I echo all the comments that have been made with regards to the concerns. Although I certainly support a REMS program, I think a critical element that's missing in

this REMS proposal is the requirements for provider learning, definitive competencies, assessment of those competencies, so that we don't come back eight years from now and say this is an inadequate program. I'd rather get it in a better place now, rather than trialing something that is, I believe, inadequate to meet the need.

Dr. Farrar.

DR. FARRAR: I voted no, and I agree with some of the things that were said by everyone and not everything that was said by everyone. So to be clear about it, I support REMS as a process. I simply think that there needs to be substantially more teeth in the process.

One thing that has not been said, clearly, training for a REMS program could also improve the overall quality of pain care in general, and I'm very excited about that as a possibility.

I think the focus on long acting is actually not a bad place to start because it does identify patients in general, currently, who are more chronic users and because of the higher dose. But at the end

of the day, it's really about dose. And I think that, hopefully, if it did start with long acting, it would have to progress to include the short-acting medications as well.

A major flaw is that I heard almost nothing about data collection. There were some general comments about how they would try and monitor and use databases and use radars and things. In fact, I think a whole new data collection system needs to be installed in order to do this and have some very specific comments about how that might happen.

I think that under the current legislation, it's possible to implement something that has a good deal more teeth, and that the pharmaceutical industry, which is the group that you're targeting, can be charged with doing things and being successful and meeting metrics in order to be successful, and that that requirement would cost a bit of money, but nowhere near the profits that are currently being made.

To do so requires making it in everyone's best interest to comply. People don't do things

unless you twist their arm, and that's one way of handling it. On the other hand, if you simply give them something that they were striving for, you make it in their best interests to do so. So we all use our credit cards and our cards at the local supermarket because we get a discount if we do so. So we give them information about us so that they know what we buy, and then they can do something with that. We can use the same when we do a REMS program.

For example, the drug companies are very good at marketing. They're able to convince physicians to use our products, their products. They can invest a little of that expertise in figuring out how to get the physicians to use it correctly and to demonstrate that they're actually successful. They measure how successful they are at marketing the product. They can and have the capability to measure whether they're successful at training physicians to do the right thing.

They're very good at giving coupons to encourage patients to use their product. Instead, you give a patient a coupon to fill out a form every time

they go to the pharmacy. They don't have to, but they get a coupon if they do. You pay the pharmacy $5 for every form they collect or data that they collect. It's in their best interests to do it. They don't have to, but they will, and the pharmaceutical companies could be held to that.

The last issue here is about the limitations of the REMS legislation, which is that I very strongly believe, after this meeting, that this group needs to send a message to our legislature, that the ability that they have given the FDA to control this problem is insufficient. They have a model, as we were discussing before, buprenorphine, which probably has problems. But if they use that model and implement it in a way to promote adequate training, not just in the safety of opioids, but in how to do it right, how to treat pain right, I think we can make a huge impact. And I think that my vote for no is clearly related to trying to send that message.

DR. KIRSCH: Dr. Nelson.

DR. NELSON: I believe education has a role in many things we do and is able to change certain

behaviors and influence certain outcomes. But as a sole measure to improve the problems that we've been discussing now for two days, I think is destined to fail. Education has a role and has some limited success, perhaps, in improving seatbelt use, in reducing smoking, but it's had devastating failures in improving seatbelt use and reducing smoking as well. So depending on your perspective on a lot of these things, education either works or it doesn't. My sense is that in this particular issue, there'd be very little benefit to doing it.

I think we really need to focus the REMS, which I do support of course, on the different factions of people that are involved. I mean, clearly the prescribers and the dispensers need to be trained, and they need to be validated and proven to be competent and capable. There are many ways that have been thrown out as a potential way to do that, including linking to the DEA and other databases. I think that the prescription data collection programs seemed like a really easy way to collect data on inappropriate prescribing and inappropriate use of

drugs, of opioids.

I think patients need more than education. I think they really need a system to work within that provides an adequate chance, an adequate likelihood that they will use their medication safely and appropriately.

I think probably most concerning to me, as I kind of alluded to before, is really protecting the vulnerable populations. When you look at the data on who abuses and who dies from these immediate- and extended-release opioids, it's quite scary when you see eighth graders and tenth graders and twelfth graders and teenagers making a substantial impact on that list. And these are people who I think we really need to protect.

In the eyes of many of these patients, in many of these abusers, opioids that we're talking about today are essentially legal heroin, and we need to think about how we would construct a REMS if we were going to be marketing heroin. And this is the patient population that we're trying to protect. Of course, I'm not saying we actually go and market

heroin, but I do think that the kind of link to the significance of this drug in the lives of people really does amount to that same level. And the population that uses it and that suffers from it is extremely vulnerable and really needs to be protected.

DR. KIRSCH: Dr. Olbrisch.

DR. OLBRISCH: I voted yes, not that this is perfect, that these REMS are perfect or will even make a difference, because we're talking about something outside. We're talking about abuse that happens outside of the population that you're meant to impact here. And I think that maybe is not within the scope of the FDA.

There is, perhaps, even some hopelessness here about whether you can impact that or whether that's in the purview of other agencies; whether it's a public health problem that needs to be addressed elsewhere or whether it's a law enforcement issue. But certainly it's not something that we shouldn't try to do.

I'm also concerned here that I hear people saying no because they think we should regulate more

in the area of immediate-release opiates. And I'm not happy to hear that because there are so many people who would be going home every day from surgery with a short-term prescription for immediate-release opiates or would not be able to do that without Al Gore having moved into their house with a lockbox.

I think that we need to be very careful about overregulation of things for which there is not the same kind of problem as there is for these longer acting. And there's a lot of overregulation in healthcare, and I don't want to see that overgeneralization happening either. But I do think that taking a first step here is worth doing.

DR. KIRSCH: Dr. Turk.

DR. TURK: Thank you. I voted no. I strongly agree with the REMS process, however, I didn't see any convincing evidence that anything that's being proposed in the current REMS plan is going to have any impact at actually making a change in the behaviors that we're concerned about.

I think I saw things that were very loose, superficial, expecting voluntary approaches which have

failed in the past. I saw no effort to consider any of the research that's available on behavior change, on implementation science, on marketing and advertising, which could have contributed to what might have gone into this plan.

Dr. Nelson mentioned the seatbelt example, and it reminded me that when I lived in Ontario, Canada, at the time that they were switching, they were adding on seatbelts, making them mandatory, for the first year that they were mandatory, they had 21 percent of the population were demonstrated to be wearing seatbelts. They then implemented a $150 fine if you were caught not wearing a seatbelt, and they had a 98.5 percent increase in seatbelt wearing. So obviously, voluntary things don't always work. Sometimes, we have to come up with some other strategies.

I understand there are costs and a burden, and I think that the public health consequences are sufficiently severe that that burden and that cost is something that can be worked out to have a more potent effect. We heard some presentations of some different

groups of some strategies that are being tried, and I think those should be things we begin looking toward.

DR. KIRSCH: Dr. Todd.

DR. TODD: I voted yes, and it was a practical decision. I'm appreciative of the time and effort that FDA's put into this process thus far. I do think it's a huge public health problem. And I believe the option of doing nothing is unacceptable, and delayed action is also unacceptable.

But I do think a limited approach is cautious; it's deliberate. And I think that efforts to change behaviors start with education, although all of us I think are in agreement that that's not enough. I do think that education regarding the use of long-acting agents will have a spillover effect to immediate-release agents; that's a positive.

I think this is the beginning, or the middle, of a longer process, and I'm very interested to hear more about efforts that are beyond the purview of the FDA and involve interagency collaboration, because I think that's where the money is. The money is in what we can do between agencies and the

coalitions we can bring together, counter-measures we can bring together through that interagency collaboration.

DR. KIRSCH: Dr. Peairs.

DR. PEAIRS: I voted yes, and I share many of the concerns of the committee members who voted no, particularly in regard to the failure to include immediate-release opioids and the voluntary nature of the education.

But in regard to immediate release, I was concerned about the practicality of including it and how that would impact the prescribers of patients and the patients who have an acute orthopedic injury or are post-operative. And I felt, perhaps naively, that the educational component could still include immediate-release opioids. So I don't see how you can really talk about one class without the other.

In regard to the voluntary nature of the education component, I find that very concerning. I think whether we reach anyone or make an impact is questionable. And certainly, those that Dr. Kopelow described yesterday, as those who don't know what they

don’t know, are not going to avail themselves of voluntary education.

But I see it as a step, and I rationalized my vote because the proposal does include a caveat that this may need to become mandatory; at least, that’s how I read it. I think this is a first step. It’s a piece of a puzzle that’s much greater, to include the public health campaign and the interagency collaboration, so I did vote yes.

DR. KIRSCH: Dr. Craig.

DR. CRAIG: Thank you. I voted no, predominantly based on prescriber education and its voluntariness, and I felt that that was an important aspect that was not included, at least in the proposal. And although I recognize the significant amount of work that FDA has done and their workgroups have done, and resources have been put forth toward this proposal, I felt that it didn’t have enough teeth as far as it didn’t go far enough as requiring education for prescribers, which I felt was very vitally important.

The second caveat, which I felt contributed

to my no vote, was the entire class of the immediate-release versus the extended-release opioids. I practice in Florida, and so I see a lot of the pain clinics, which have been brought up here. The number one drug that they prescribed is immediate-release oxycodone.

So I felt very strongly that if we're going to try to address the problem of addiction, overdose, and death from opioids, that it should include the entire class. And I understand the mountainous effort that would be required to include the immediate release. In addition to the extended-release opioids, I felt that it should be more of a class effect versus carve out for the long-acting or the extended-release products.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: I voted no because I think that in both briefing materials, the presentations, and in the constructing of the REMS, the FDA failed to adequately acknowledge what really has brought us here, which is the education campaign, criminally conducted by Purdue in the '90s, which led to this

huge increased use of dangerous, more dangerous than immediate release, extended-release opioids, Oxycontin specifically. What is to be learned from that is deficiencies in advertising, deficiencies in letting the education be done by a company, which is part of this program, and so forth.

So I would have liked more, since the FDA spent a year or two developing this, for them to have come here, not only with what they could do within existing REMS, but as John Farrar pointed out, a critique of existing REMS, and saying we would support -- and obviously would have to have gotten department clearance and so forth, but there should have been enough time to do that -- we would support an expansion of REMS to include, for instance, civil monetary penalties for all advertising, not just that.

They could have also in that period of time cleared to the department the idea that a mandatory educational program, as involving mandatory DEA connection with the education on this, would be supported.

In terms of retraining -- I've used that

phrase before, because I think at least that part of the problem -- that's the extended release -- involves retraining people back to where they were mistrained before they were mistrained in the late '90s and the early part of the 2000s.

So I think parallel to and a necessary complement to the REMS -- I also support REMS' expanded authority particularly. But complementary to it would have to be these other kinds of efforts, that they say, yes, we can do this much under REMS. We have already initiated the effort and gotten the department and the White House to support legislation that would bring the DEA part there. We've also done some other things so that we can do a much better job monitoring the industry.

Nobody thinks, even in the most expanded form, that REMS itself is going to do it. It is necessary to have REMS. I think that this could have been done better than it was, and I think that the education of this committee could have had much more of what lessons were learned from the disaster involving Oxycontin.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I voted no because we were asked to vote yes or no on the entire question. First of all, I want to thank the FDA for bringing a very important public health concern to the forefront and bringing this panel together. I think it's crucial that we discuss the issue and come to a resolution.

I am in favor of the REMS process and strongly support it. I think the devil is in the details, and the details we were asked to look at today don't go far enough.

What would make me vote yes, as Dr. Vaida said. I think that first and foremost is training, not voluntary education. I'm the chief quality officer for our hospital and find that throwing education at people in the daily stream of their work means that it's bypassed. Training is an important part, and mandatory training of prescribers and pharmacists, prescribers, and dispensers, I think is important.

We said that this was a public health issue, and public education or community education really

should be part of this as well. And it was pointed out that that is an effective component of the total education intervention triad.

The education really should be targeted for the audience or for the at-risk population, which is identifying the ethnic groups that are particularly at risk and the SES groups that are particularly at risk; and finally, making sure that we have a reasonable impact analysis so that we can follow and adjust the REMS as appropriate.

For the record, I'd request that the comment on Al Gore be stricken from the record. Thank you.

DR. KIRSCH: Dr. Porter.

DR. PORTER: I voted no, but with reluctance. I think this is an incredibly important program that should move forward without undue delay. I think the FDA has done a great job in getting started with this, pulling together a lot of really useful information and really setting a good foundation of what needs to go forward.

I think that the cost to the healthcare system, the burden that this kind of a program would

put on the stakeholders, including the sponsors, the physicians, the pharmacists who would have to go through the educational components, as well as the patients and the victims of diversion, would all benefit incredibly from a successful program. And so the benefit, if the program is done properly and is successful, could definitely outweigh the costs and the burdens.

The reason I voted no was that I thought the breadth of the program needed to be expanded, that the immediate-release opioids should be included. I think, on their own, they cause enough of a significant healthcare problem that, even if we weren't considering or there was no existence of the long-term acting drugs, that they should have their own REMS program.

I also thought that the educational component wasn't sufficient, that the training of the physicians should be mandatory and that the public educational programs should be really expanded to a large public health education campaign in order for the program to be successful.

So it's the scope, the mandatory nature of the training, and that the details, again, some things that might be included were better management of the drugs as far as storage, as far as identifying abusive prescribers and abusive consumers, that those are things that need to be sort of carefully detailed in advance. But I would like to, again, reiterate that this is something that should be expedited. The process, hopefully, will not be delayed by the no vote.

DR. KIRSCH: Dr. Flick.

DR. FLICK: I'd like to thank the chair and the FDA for the efforts that they've put into this. I think this has been a highly valuable discussion. I voted yes, not because I believe or have confidence in this REMS to have an impact; in fact, I voted yes because I have confidence in its failure. And I think that failure can be useful in bringing the agency and others to the realization that this problem is broader than something that can be approached by FDA. It needs to be approached in a more broad, comprehensive manner.

My concern is that we have voted this down, and we'll be back here as a committee in a year, looking at another REMS, created by FDA, within a regulatory environment that does not allow them to clearly address the issue. So, in fact, we will have delayed a process that really needs to move forward to become more comprehensive and inclusive.

DR. KIRSCH: Dr. Beardsley.

DR. BEARDSLEY: I voted no. I'm very much strongly in favor of the goals of the present REMS, but I just didn't feel that the proposed provisions will improve public health. I didn't see much data in support of any of the proposals, which I think underscores the need for pilot data to make proposals in the future, provisions in the future.

I wasn't confident that there exists baseline data to assess the effectiveness of any of the proposals in the future. And the whole idea of proposing multiple manipulations at one time, none of which really have adequate data to support them, would make future assessment impossible of any of the individual provisions.

Also, I was disappointed that the immediate-release opioids were not included in the present REMS proposals. As I said earlier, as I mentioned earlier, I think if it's not, then we're going to be back here in the near future with a REMS for the immediate-release opioids for themselves.

Finally, I thought that there needs to be an explicit way of behaviorally assessing the prescriber for his or her behavioral change, not just providing educational materials, much of which the information is contained in existing package inserts. But there needs to be an assessment of behavioral change that the prescriber has actually been trained to adjust his or her prescribing practices of the future so as to avoid the kinds of consequences that we've been talking about today. Thank you.

DR. KIRSCH: Dr. Morris-Kukoski.

DR. MORRIS-KUKOSKI: I voted no, and most of my sentiments have already been echoed. A couple reasons why that I'll just point out. One is the voluntariness for the education component. I believe that this is a very serious issue. I do believe in

the spirit of a REMS. But I do believe that education should be mandatory, and not just education, but training as well, to not just physicians, but all healthcare professionals.

We also need -- without looking at the component of other interagency collaboration, we're stuck with potentially educating and training people better so we can have decreased drug-drug interactions, and decreased adverse reactions based on drug disease, but we're still stuck with this big subset of a population that is misusing and abusing these substances. They are the people and they are the group that wind up being the overdoses and the toxicity. Without somehow regulating these physicians' bad practices, and regulating the pharmacies' bad practices, to continuing to fill these prescriptions, we're not going to have the end result that we want.

DR. KIRSCH: Dr. James Woods.

DR. J. WOODS: I voted yes because I felt it was necessary that we do something. I felt that the REMS is a good idea and insufficient to handle the

problem that we face. But I felt it was necessary to vote yes anyway, irrespective of its imperfections. Otherwise, I agree with just about 80 percent of the considerations that have been raised by those who voted yes and no.

DR. KIRSCH: Okay. We're going to go onto the next question, question 4, which reads, "Please discuss how we should work with sponsors to develop the necessary educational program for prescribers and patients. Include the following in your discussion.

First, how this might be achieved to avoid the concerns that have been raised regarding the manufacturers' involvement in the development of these tools; second, the value of a common set of educational materials for all products versus individual product-specific material, and third, potential initiatives to improve prescribers' participation."

Dr. Farrar.

DR. FARRAR: So I think it's important to understand that, at least, I think that it's possible to do this. However, there has to be a wall

constructed between the funding of the effort and the material that's then conducted in the effort. There are examples of this.

The first part of this question is how might it be achieved to avoid concerns raised about regarding manufacturers' involvement in the development of these tools. And what I would argue is that the IWG is a great organization. They ought to contribute the funding based on a certain payment per prescription written or something like that, and that there would then be set up a group of academic or knowledgeable experts who would receive proposals on how to conduct that education and make informed decisions about how to go about providing that education. So I do think that it's possible to do that.

I think there is value in the common set of educational materials, however, every person requires specialization. And so I think it would be really in the best interest of all groups to target the education based on the underlying knowledge of that group.

Also, frankly, someone suggested excluding certain groups like the people sitting around the table or people who are pain trained, and I'd actually argue against that. As much as we like to think that we know what we're doing, some of the more practical aspects could use some reinforcing and a little bit of updating on a five-year basis. As a requirement for my DEA license, that would make a whole lot of sense to me.

The potential incentives to improve prescriber participation, honestly, I think it needs to be required.

DR. KIRSCH: Dr. Ballantyne?

DR. BALLANTYNE: I actually agree with a lot of what Dr. Farrar just said. I think if we examine the failure of previous REMS, I would say that a lot of the failure can be put at the feet of the continued role of the drug companies in providing education about pain management, and that role actually became predominant to the point that many people around this table were concerned that the educational message was biased by the role of industry. In fact, I would say,

in my lifetime in pain management, there is no doubt that most of what I learned came from industry-sponsored education.

So I think that I agree with Dr. Farrar in that there needs to be some mechanism to put a wall between the drug companies, or the sponsors, and the people providing the education, which doesn't mean that they shouldn't be involved, but that there should be some mechanism to get between them and what ends up being the vital educational message.

In terms of part B, the common set of educational materials, I think it is a good foundation. Obviously, it needs to be modified according to who you're educating. But I think there are some fundamental principles, and it would be valuable to set them out.

In terms of incentives, I agree with many other committee members that it needs to be mandatory or it won't get done.

DR. KIRSCH: Dr. Nelson.

DR. NELSON: Maybe I kind of commented on this earlier. I really don't think that the system,

the way it's currently set up, is tenable at all. And I think that there should be some real effort placed by FDA into trying to see if we can't regulate this out of existence, such that FDA's charged with creating this broad educational material and not getting somebody else to do it and not giving that role to the sponsors. And that's the colloquial, the fox guarding the hen house, so to speak. It just seems to me to be a poor place to be.

If it has to be that way, then it would seem that the wall would be okay, but I would like it to be more than a wall, maybe like a ravine or an ocean or something between the two companies or between the two.

I guess one of the thoughts I've always had about CME, and the thing that's always troubled me is when you're given money by a company to produce something, and you have no obvious conflicts, the conflict that's built in there is the next contract that you're going to try to get. So you have to kind of satisfy the company to get the next contract.

So it would really be nice if that money

that they had allotted to do this was set aside and really used in a real, no-risk kind of way, that the people involved have no chance of satisfying the company in any ways, that they're not looking for the next contract. And their whole goal is to create a very valid set of educational material that could be used by providers and patients, whoever it's going to really be directed for.

I really think that rather than touting the benefits of the drug, if we really use this as a risk management tool, it should provide the other side of the coin. It should focus a little bit more on the risks, perhaps, because this is not promotional material to sell the drug; this is material to assure safe use and appropriate prescribing.

So I think the focus of the material has to be really set properly and has to be vetted through FDA and whoever else needs to do that. And incentives to prescriber, I mean, I think the only answer's going to be to mandate it.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: One of the elements that was, at

least by this committee, voted down, in this package called REMS, is the medication guide. And this comes to mind because it sort of overlaps with the parts of question 4. There is no reason why the FDA can't develop a medication guide. There was a debate yesterday whether there should be one or three or whatever else. But a medication guide that's FDA approved, vetted, does not have to have any significant input from the company because by definition -- I mean, we've been involved in this kind of issue for about 30 years.

The FDA has the authority to require medication guides for certain dangerous drugs. Right now, maybe only 4 or 5 percent of all drugs on the market have medication guides. The other information that people get is just sort of willy-nilly, inaccurate. The FDA's done several studies showing how incomplete it is. So FDA has the authority and has recommended under REMS to do a medication guide. I think that would be very useful. It could be greatly increased, in terms of what it has in there, as opposed to now.

As far as the role of the companies -- and I'm not sure FDA has the authority to say to companies, "You put up the money, but we're going to have complete control over what's done with it." Ideally, that should be the case. It's a matter of undoing a lot of the damage that's been previously done, not just by Purdue, as I can keep focusing on, but other companies as well. You need to undo a huge amount of malicious education that's been done that has caused this kind f problem.

So I think, in terms of going beyond the medication guide in the way this is proposed, the FDA, outside of REMS in the safe medicine use talked about several things that they were doing. We would certainly welcome at least some of those, not as a replacement for the mandatory kinds of thing.

Again, part C, it has to be mandatory in terms of both the pharmacists, physicians or any other prescriber; otherwise, it's not going to work.

DR. KIRSCH: Dr. Jenkins.

DR. JENKINS: I'd like to hear some feedback from those members of the committee who have mentioned

that you think the training, education, whichever you prefer as the term, should be mandatory.

Are you thinking in context of the legislative requirement to be linked to the DEA registration, or are you thinking in terms of our REMS authority, where we would be working with the manufacturers to set up basically a system that prescribers would have to enroll in and be trained and certified in order to prescribe the drug, say, along the lines of isotretinoin?

It'd be useful for us to know, are you thinking legislative solution, linking to DEA registration? Are you thinking we should try to set this up as a parallel system through the REMS authority?

DR. KIRSCH: Dr. Berger, if it's to address this particular issue.

DR. BERGER: I would say, even whether through DEA or even through your licensure, would be the easiest thing to do. Then it doesn't have to go through FDA.

DR. JENKINS: Just remembering, licensure is

a state-based --

DR. BERGER: Then do it through DEA. That's how people have to write their opiates.

DR. JENKINS: Okay. So you're advocating that it be mandatory --

DR. BERGER: If it's possible, that would be the dream to do.

DR. JENKINS: Okay.

DR. BERGER: I mean, if it's a possible thing, that would be my wish. Whether that's true for people around the table, you need to ask that question. But that would be the dream.

DR. KIRSCH: I'd like to comment, actually.

So I'd like this not to be used as an excuse not to do it. So you all are the experts to know whether it's easier to do it through the REMS mechanism or to do it through the DEA and have legislative action. But it'd be my interest not to use this as an excuse. And if it's easier, mostly under your control, to do a REMS mechanism, then my request would be to have it done through the REMS process.

Dr. Kerns.

DR. KERNS: I actually remember Dr. Rappaport, I'm pretty sure, saying that it could be done within the legislation by FDA, but that it would be easier, and if there was a change in the legislation that allowed DEA to do this.

So I actually very strongly agree with the statement that was just made that this should be done by FDA and take steps to develop a method for mandating it and registering it now.

DR. KIRSCH: Dr. Flick.

DR. FLICK: Dr. Jenkins, correct me if I'm wrong. If this was done outside of a federal agency, like DEA, then FDA could require the sponsor to require the prescriber. FDA can't do that. It can require the sponsor to mandate education.

Is that right?

DR. JENKINS: I'm not quite sure I'm following the question. The way it would operate, if we were going to do it under the REMS authority, is we would require the sponsors to develop a training program and an enrollment system through which

prescribers would have to receive the training, become certified, and then you would have to link that information to the pharmacy to say that unless they have been enrolled and certified in the program, you can't dispense a prescription for whatever product you decide should be covered, be that extended release, long acting, or the entire class, similar to isotretinoin.

With isotretinoin, you have to be enrolled in the iPLEDGE Program. You have to be trained and certified and enrolled. And when your prescription goes to the pharmacy, they will not fill that prescription unless you're enrolled in the program.

That's how we would do it under the REMS authority versus the DEA authority where it would be you can't get your registration number to write the prescription that the pharmacy's going to fill unless you've completed a certain amount of training. Pharmacies already have the ability to check that your DEA registration is valid.

DR. FLICK: So as a prescriber -- and it is, I think, the statement of this committee that it

should not simply be long-acting narcotics; it should be all narcotics. So every physician in the country, then, would have to be given permission to write prescriptions by sponsors for opiates, and I don't think that anybody in this room really wants that to happen.

DR. KRANTZ: I don't think you speak for all the other committee members. With all due respect, I think some of us are okay with allowing folks to write for short-acting opioids. As a cardiologist, for example, I can't --

DR. FLICK: No. But I --

DR. KIRSCH: Let me clarify that.

DR. FLICK: Yes.

DR. KIRSCH: As I understand, what Dr. Flick is saying, Dr. Flick is advocating that the sponsor should not be the group that determines whether or not we as prescribers are able to write the prescription for a particular medication.

DR. FLICK: Exactly. And that is what Dr. Jenkins is telling us. It's that is the REMS system. That is what the legislation requires, is

that if you or I want to write for methadone or Oxycontin, we would have to have permission, so to speak, from the sponsor.

Dr. Kirsch, correct me if I'm wrong, but the committee has already expressed its sense that this REMS should apply broadly to all narcotics. So if we follow those statements to their conclusion, then every physician will have to go to a sponsor to be allowed to write for an opiate.

DR. KIRSCH: Dr. Jenkins.

DR. JENKINS: Just a little bit of clarification. The requirements for what the training would be and the certification would be, under the REMS, would still be approved by FDA. So we would be saying what the requirements are. It would be the sponsors who would be standing up the system to implement that training and collect the information of who passed the test or whatever certification there would be.

So we would set the standards for the certification requirements; they would have to stand it up. So it's a little bit different from saying it

would be the sponsors who would be determining who could prescribe. They would be running the system. We would be setting up the standards.

DR. FLICK: But this would be an entirely new system in parallel to a system that exists currently?

DR. JENKINS: Exactly.

DR. KIRSCH: So to summarize Dr. Flick's opinion as I understand it is that he feels strongly that this authority should happen through the DEA and not through the REMS program.

DR. FLICK: Well, I think that that almost goes without saying, that the cost of this would be borne by our patients and by us. And it would be extraordinarily expensive and cumbersome, and would seem to be somewhat unnecessary since a system already exists.

DR. KIRSCH: Dr. Markman.

DR. MARKMAN: I think one argument for having this be -- two arguments, actually, for having this administered and reside within the FDA under the REMS authority is I think, number one, as we've talked

about and was the discussion earlier with regard to advertising, if it goes through this mechanism, in contrast to advertising, the FDA will be, in a prospective way, able to control or to regulate the content to some extent; whereas with advertising, that can only be done retroactively. So I do think here is a proactive mechanism for the FDA to be involved with controlling the messaging up front.

The second reason, presumably the FDA has the deepest understanding, and I think the agency certainly does, of many of the risks that go into not only the application but also into the phase 4 issues around these drugs. And I think to link the understanding of the phase 4 complications that are being collected in an ongoing way with the education is critical. And if this does reside within the DEA, they will basically have to go to the FDA to understand what the phase 4 issues are.

So I do think, in terms of the education coming from the experts with the deepest repository of knowledge about the compounds and about the ongoing real world implications of having those compounds out

there and being prescribed, the FDA is the natural home for this educational forum. I do understand the challenges that Dr. Flick raises regarding how cumbersome would this be and the fact that there would be duplication. But with regard to the specific content that prescribers need to have at their hands, which will inform the messaging on an ongoing basis, I think the FDA is a logical home.

DR. JENKINS: Just one point I want to add to that. The Drug Abuse Treatment Act did provide a role for SAMHSA in the content of the training that was required to get that special DEA number for outpatient treatment of opioid dependence. So there's nothing to say that legislation linking training to a DEA registration couldn't also have FDA in a role of helping to develop the training. So you could have both if the legislation were written to provide for that.

DR. MARKMAN: Hearing the rationale for the many members, or the several members who voted yes, their concern was that they felt a yes vote was a way to expedite some intervention. And some intervention

was better than no intervention, or the delay, as someone said, would be unacceptable.

So I think my only fear with letting the legislative process and that timeline drive this, is that, frankly, that could be a decade before that actually happens. I don't think a decade is acceptable to the yes voters or the no voters here. So to the extent that the DEA option requires a decade's worth of wait, I think it's not acceptable, from my point of view.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: What I'm hearing here is a partnership. The part that is the check off by the company as to whether a doctor can write a pill is I think ridiculous. For isotretinoin, it's fine. It's one product. Here, we've got a dozen or two dozen companies and who knows how many different products there?

So again, I think that to wed the expertise, the unbiased expertise of the FDA and/or SAMHSA or whatever, with the authority to do the check off with the DEA, is I think a more logical way of doing it.

I was just looking at my notes, when Dr. Rappaport at 1:00 yesterday started off by saying, "The REMS does not have the following." The first thing was electronic verification of doctor training, because, he said this would be too difficult, complicated, whatever else, and then, he threw out -- which is why I asked him whether he supported it -- the idea of it going to DEA.

So I think the combination of the educational materials being developed by FDA, NIDA, SAMHSA, and then put into the training program, which someone would have to do in order to get their DEA license, would be something I would agree with, and I would wonder whether other people would agree with this as well.

DR. KIRSCH: Dr. Nelson.

Dr. Deshpande.

DR. DESHPANDE: I want to come back to Dr. Kirsch's point that we don't want to have this question delay a revision of the plans; that if the FDA has the authority through REMS, then I would recommend, as Dr. Markman also pointed out, that we

need to move ahead because this is a public health concern. And, therefore, if it can be done under the REMS authority sooner, while working with the other agencies for an eventual legislative fix, then it definitely is worth doing. And I think Dr. Vaida and several of us said that we would have switched our votes to a yes vote if mandatory training was included as part of the REMS.

DR. KIRSCH: Dr. Berger.

DR. BERGER: I would vote that industry definitely be kept out of training. And some form of ACCME, the pharmacy, ACCME, be used. In terms of a common set of educational materials, that's not very hard. A group of experts -- there are tons of educational tools in terms of opiates and pain management things already out there. Not hard. There are lots of organizations already doing tons of teaching. It would be very easy to pull together with groups of experts.

I think we just definitely need to keep industry out of it with using an ACCME-type model and clearly with potential incentives. It absolutely must

be mandatory both for physicians and for pharmacists, and for NPs and anyone involved in the prescribing and dispensing model.

DR. KIRSCH: I'm going to take the chair's prerogative and try to summarize what we have so far, and see if we can move onto question 5.

So we're intended to discuss how we should work with sponsors to develop the necessary educational program for prescribers and patients. I think, my sense from the committee is that as a committee, on average, we're uncomfortable with industry or the sponsors creating the educational program of understanding the needs of the FDA.

I think the committee would feel more comfortable if FDA created the content of the training or education program, or if necessary, to include the sponsors, to assure that extensive review occurred prior to approval for general use.

How this might be achieved to avoid concerns that have been raised regarding manufacturers' involvement, again, the best way to avoid it would be to have content developed by FDA in consultation with

experts in the field, but if necessary, to have the sponsors involved to make sure that before released in a prospective fashion, to have extensive review and ultimate approval.

I think the committee as a whole does value a common set of educational materials for the products or groups of products, rather than having individual educational materials for individual drugs. And I think overwhelmingly the committee believes that there is no need for incentives to improve prescriber participation, but rather this education or training should be mandatory, working either in concert with the DEA or through the REMS legislation.

Now, with that as a summary, I'll take additional comments.

Dr. Morrato.

DR. MORRATO: I didn't get a chance to add a bit. With regard to how to organize, I agree with what's been said in terms of a payment model that's like iPLEDGE. And there is just two points I wanted to say.

One is how do you figure out what's a fair

payment? We talked about linking it with the market shares, et cetera. But I think we should consider what is a standard promotional spending to do an adequate education program. So it's not a standard of what we typically have in federal grants to do an NIH study. It's not the standard of a public health program that's trying to scrap things together. It needs to be of a standard of funding that industry uses to do their advertising materials.

The other piece I just wanted to say is that I think it's important to bring experts from academics, but I think we also need to bring expert stakeholders who, as we've heard in the session, have a tremendous amount of practical hands-on experience designing these kinds of programs.

I would be careful -- I know we need a barrier, but I would be careful in throwing out the baby with the bathwater, in that many in marketing and advertising agencies have this very skill set that we need to be applying to these kinds of questions, with state-of-the-art knowledge, as well as the CME developers, of how to actually affect change. We can

keep barriers, but I think we don't want to totally exclude all of that expertise and hands-on knowledge.

And then with regard to -- I actually voted yes, so I just wanted to throw out that I think there are some incentives that you can do. In light of yes, it's important to institutionalize, you know, as we've been talking about the mandatory. But I think audit feedback, which we heard from I think the Missouri Medicaid program -- and systems like that have been used as ways to make visible what behavior change you're trying to do.

So the National Surgical Quality Improvement Program was trying to reduce mortality following surgeries. And they did an audit kind of program that was described in which you would see how your hospital ranked on this measure relative to others in your competitive set, if you will. And you actually do real-time tracking of what percentage of physicians in a particular region or particular specialty type have signed up for that, and you publish it weekly, so it's very visible. And you start tracking. Just like when you have a target campaign to raise money for some

sort of charity, you make it visible what your target it, and you make it visible how you're tracking against it, and you use the natural competitiveness of folks to not want to be the ones left out.

So we could create sort of surveillance maps in the same way that CDC uses maps to look at behavioral risk factors, survey or tracking obesity. Instead of those, we're tracking compliance with this kind of training.

So I'm not discounting that, yes, institutionalizing it by making it mandatory is obviously where you'd like to be, but there can be things that are done in the meantime.

DR. KIRSCH: Dr. Carter.

DR. CARTER: Yes. I just wanted to point out that 4B is phrased as a choice, and it might not have to be. There might be a possibility to allow a common set of materials and product-specific materials. The concern being is that with a common set, there may be an incentive to simply achieve a minimum. And there might be pathways or incentives that could be provided to allow that some companies

are looking to do something more innovative so that innovation is not stifled. But there may be a possibility to allow product-specific materials to try and improve this sort of approach.

DR. KIRSCH: Dr. Krantz.

DR. KRANTZ: I would agree completely. I think, in my mind, the framework that the industry working group laid out were three choices, the fentanyl, the methadone, and the long acting seemed a logical one. In my mind, for example, methadone is the only one I'm aware of that has significant cardiotoxicity. So to sort of lump it all together would really be very difficult and perhaps not in the patient or the physician's best interest.

So I would consider the question as do we decide whether we like the framework as proposed by IWG, and if so, how we move ahead.

DR. KIRSCH: Dr. Ballantyne.

DR. BALLANTYNE: I just wanted to comment on the way that you, Dr. Kirsch, just summarized how the committee feels about this. I think it would be very different if it only applied to extended-release

opioids, because then it would have the undesirable effect of people being trained to use these drugs, but in many cases preferring to use the drugs that were not controlled in this way because it's easier.

DR. KIRSCH: Dr. Porter.

DR. PORTER: So I don't have an answer to this question. I don't know that there is one. But how high is the wall between having sponsors enroll and going through the DEA?

Is there any creative way that there could be a partnership set up, where you don't have to actually set up the legislation to go through the DEA, but somehow, that information could be fed into them through something that the sponsors were to establish?

DR. THROCKMORTON: I guess I'll just say that we have had discussions with our legal colleagues, who are not here, and we've been told that legislative change would be required.

DR. JENKINS: Basically, somehow, you have to set up a system where you can't prescribe the products unless you've had the training. One way is to link it to your DEA registration. The other under

the REMS would be to set up an isotretinoin-like program. Those are the only two ways that we're aware of. And currently, we don't have the authority to the DEA link. That's the legislative requirement.

DR. KIRSCH: Dr. Olbrisch.

DR. OLBRISCH: I'd like to add that there are other aspects to pain treatment and pain management besides pharmacological, and that these should be components of any educational program for physicians. And when you focus on the role of industry, you start limiting yourself to pharmacology.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: I just want to briefly mention the last part of the statement that said the DEA or through the REMS. And I think we heard that we would rather maybe not have it go through the REMS; there may be too many manufacturers in that.

Just that the FDA's aware too, and I'm sure you are, is the DEA, that would be limiting to prescribers. I do not have a DEA number, and nurses don't have a DEA number unless they're nurse practitioners and prescribe; so other healthcare

professionals. So if you want to say DEA, or, ideally, it'd be the licensing bodies, because in order to get my license, medical license or pharmacy license, we need to have CE, and they could mandate what CE we have. So I'd just like to get that out and clarified, because there's so much emphasis on that DEA number.

DR. KIRSCH: I'd like to remind the committee that our comments are taken very seriously by the FDA, but our comments are advisory, not prescriptive, to the FDA. And so, I think it's important that they hear us, but we're not going to be able to define how the FDA actually acts on this matter or any other matters.

Dr. Denisco.

DR. DENISCO: It's being commented that there's only two ways to accomplish this, one through the DEA, and two, through a sponsor-organized registration plan.

There's a third way, and that's through the Federation of State Medical Boards. Now, there's no legislative way to adopt it, but they are very

interested in this problem. And if they were contacted, might well be glad to put this on as a CME requirement, much as was discussed as with the other boards, because to keep throwing it into the DEA, when the DEA has been involved with the buprenorphine issue, they've been heavy handed recently in the inspections. And they've admitted they've done this and are going to be more respective of physicians' rights.

So before it's advised to use the DEA, I would urge a lot of caution and think of considering the Federation of State Medical Boards, which as of yet has not abused its powers.

DR. KIRSCH: Dr. Jenkins.

DR. JENKINS: We have had lots of discussion with the Federation of State Medical Boards. We met with them recently, and I know they testified during the open public hearing that they're very interested in playing a role. There are 70 individual licensing bodies that are represented by the Federation of State Medical Boards. So as I understand it, each of those 70 would have to adopt the requirements if you wanted

it to be universal across the country. Not saying it's not an approach, but the Federation is just that. They're a federation. They don't have any overarching authority over their member organizations, so you'd have to work individually through the 70 members. But it's clearly a pathway that we're interested in. We've been discussing with them linking training to licensure for your license to practice.

Let me mention one other thing that we haven't talked a lot about here, but it is important to bring this up since we've heard a lot of calls for expanding the REMS to include the immediate-release products as well.

While we presented this to you as a class REMS for the long-acting and sustained-release products, in reality under the law, we will be imposing a requirement for REMS on each individual sponsor that has an application for those products, and we've encouraged them to work together collectively. And for each individual product, we have to meet the statutory framework for being able to impose a REMS.

When we start bringing in the immediate-release products, you have a lot more products, a lot more sponsors, and we'll have to meet the statutory triggers for new safety information for each of those products as well. So it's not as easy as it might sound to say a class REMS, that you go from long acting and sustained release to the class of all the immediate release because I don't remember how many applications there are, but there are many, many more applications and sponsors, and we have to meet the triggers under the law for each of those applications.

So it is a big step from the legal standard to go from extended release, long acting, to immediate release, and that's part of why we chose not to include it in our plan. It's not the primary reason. The primary reason is we thought this is the major problem we were seeing with the product itself, having an inherent risk of the high dose, the sustained-release mechanism that could be easily defeated, and even in a legitimate patient cause a fatal outcome.

But I just wanted to make sure you're aware of that. It's not as easy as it sounds to go from the

constrained REMS that we've proposed to including all immediate-release opioids.

DR. KIRSCH: Last comment on this question is going to be Dr. Peairs.

DR. PEAIRS: I just wanted to say that if changing this to a mandatory education occurs, to me, that's a game changer, as far as leaving out immediate-release opioids. The way the proposal is written now, there really isn't a reason for a squeeze-the-balloon effect, where prescribers are going to shift to prescribing short acting. And as much as I think it should be mandatory, if I saw that proposal, I would vote no unless it included immediate release, because I think there would be a lot of unintended negative consequences to that.

DR. KIRSCH: Okay. Thank you. We're going to go onto question 5.

Question 5, I'll read. "Please discuss how to assess the impact of REMS. Include the following in your discussion: specific metrics that should be used, and sources for data on those metrics; the changes in those metrics that would constitute

evidence of success for the REMS; the changes in those metrics that would suggest a need to make changes in the REMS; the appropriate period of follow-up for initial evaluation and to determine if the REMS is working; how to distinguish the effects of REMS from other efforts to address misuse and abuse of these analgesics.

Dr. Farrar.

DR. FARRAR: I've said earlier, and so I won't repeat, but the collection of data is an absolutely vital part of this and is one of the devil's in the details piece of it.

I wanted to make sure that it was clear, that it is very important, from my perspective, that a whole new set of data be arranged to be collected -- we do not have adequate measures currently -- and to be very specific that the data needs to be focused on the various categories that we have been talking about and that sometimes continue to get jumbled up in terms of considering how to affect the overall process.

Because, clearly, affecting how patients are prescribed medications, and even if they stored them

better and disposed of them better, there is still going to be a large number of patients, or a significant number of patients who get medications in Florida or elsewhere and will need to be dealt with in a very, very different way. So that the global measure of how many patients die because of overdose may not completely reflect the effects of the process.

It's specific, just to be very clear about it. I think that the information presented by Dr. Dormitzer about where people get their pain medication is an important slide for us to focus on, because it helps us to know where to focus the efforts that we undertake.

In terms of the metrics to use, to state it again, I think it's absolutely imperative that you get patient-level data on their use, or at least on their storing and on their perceived use of their medications. That data is obtainable at the source of the pharmacy. It is obtainable without requiring that they do it. It is obtainable by making it in their best interest to do it, as I said, by giving them a coupon for $5 off their co-pay and providing a $5

payment or some amount of money to the pharmacy for collecting those forms. I would bet that you would get substantial data that would help us to actually understand whether these medications work and also to say do you keep it in a safe or something.

Those questions and how those questions would be asked would have to be very short, have to be something to be completed very quickly, and could be changed over time, and should be generated from the FDA or from some organization that wants to define what needs to be known in a way that makes sense.

Clearly, in terms of the overall metrics, we've had a lot of data presented here about the number of deaths. and I think our ability to understand that is clearly growing. The one thing I would argue is that we heard in the public presentation the concept of actually labeling, being able to label pills.

For those of you who know me, I am inherently paranoid about the amount of information that's being collected on all of us. And what's very clear is that there's no limit to the amount of

information that can be collected on all of us -- all we need to do --so what we need to focus on is how that information is used.

Carrying that forward, if every pill is labeled with a little identity tag, then when a thousand Oxycontin are identified in a car, we know where they came from and we can do something about that. So I would argue that that is an important additional data source that is necessary for what we do.

Then in terms of the number of patients that die because of opioids, I think we talked before about the need to provide guidance at least and to do serious work about trying to figure out whether the opioids were simply there when they died or were the source of their death. And I think it's very hard to know. And it may be that we can't know that. But at least, we ought to be honest with ourselves to say that even death data is going to be sometimes hard to interpret, and we at least need to understand the variability there so that we can interpret it better.

Then, in terms of how often it should be

collected, honestly, it's an ongoing thing. I think there ought to be a dashboard that comes up and changes on a weekly basis, based on the data that's collected. There's no reason in the world, given the current ability to collect and move data in the marketing world, that we can't do it better in an attempt to try and improve care.

Then, the last question was distinguishing the effect of REMS from other efforts. Honestly, you're never going to be able to dissect that out. If things get better, everybody gets to claim credit, and if things get worse, we know it didn't work; that, with the stipulation that we would look at and dissect the data into the different groups that we were discussing before, i.e., unintentional overdose, purposeful overdose, drug abuse by drug abusers, and sort of the party, grab a pull out of the bottle-type of phenomenon. Thank you.

DR. KIRSCH: Oh, my gosh. I thought there'd be a million hands up for this one.

Dr. Nelson.

DR. NELSON: These are obviously very, very

complicated issues. The current sources that were presented here to provide data for us are all ongoing, and they have a long track record, which allows us to follow trends. Obviously creating a new data set would mean that you'd have essentially no track record, which would make it hard to know what any directional change meant, although obviously, you might be able to gauge up or down or something like that. It would obviously be very limited.

The one thing I thought that was really interesting, the hardest piece of data you have always, is death data. And John's comments were right, which is it's very complicated to figure out whether somebody died of a specific drug or whether it was incidental in their cause of death or in their death, period.

One thing that would be interesting, and something that's been talked about a lot in the med tox world and the forensic toxicology world, is trying to define a lot of these things and put some quantitation around meanings of numbers and post-mortem redistribution values and some things like

that. And as best I know, nobody's ever really taken the lead in trying to organize this type of symposium or this sort of consensus discussion.

So this might actually be something that would be useful to think about, which would really be trying to figure out -- it's hard, but it's something that's potentially possible; but bringing together a group of people that would actually be able to set some definitions and standards about interpretation of, I guess, pre- and post-mortem drug testing when it comes to the opioids.

The other things I think, obviously, are much more complicated. but death is definitely a hard endpoint.

DR. KIRSCH: Dr. Terman.

DR. TERMAN: I guess I'm not terribly surprised that we're having a little trouble with this metrics question when we've changed the whole idea of what we're doing. Now, we're including immediate release or now we're including mandatory education.

So, of course, the metrics are going to change somewhat. If there's mandatory education, then

what you're going to be looking at is how many people opt out of bothering with the DEA certification, for instance, deciding not to treat patients with pain.

When the FDA talks about that really the only thing they can do is to hand it back to industry for mandatory education, that sounds like more involvement of the industry in the education to me. In fact, what I'm really hearing is registries. And after reading hundreds of pages of people who thought that registries was not a good idea, after industry actually coming together as a working group to work on this, to send it back could destroy the industry working group in terms of actually working together. Now, you've got everybody for themselves, which I was actually kind of excited to see, for a change, was not taking place.

Now, I could be wrong on that. But it sounds like when the FDA's talking about what they can do without the DEA, without the medical boards in each state, all they can do is kind of tell the individual sponsors to do what's right and make sure there's education.

So, I think dealing with this metrics question, when we've changed the whole landscape of our suggestions, I for one am still very much against registries, and particularly for each individual product. That's a nightmare for treating my patients.

DR. KIRSCH: Dr. Kosten.

DR. KOSTEN: A few things. The first is that I'm afraid I disagree with this issue of getting the DEA involved or not involved. I think there are examples, particularly with Actiq, these fentanyl lollipops, of where the FDA did in fact have a process where they directly did interventions that have had a very nice impact on people don't abuse the lollipops very much. And that did not involve the DEA.

So I think they can do it if they want to. I think the persons who need to pay for it are the industry. I think it's very clear that they can extract money out of industry to get drug approvals; they can extract money out of industry for this.

I think that doesn't mean they don't control it. They do in fact control it. They control the standards. And in fact, one of the other things that

I think that they do control, and that they should insist upon, would be the audit and feedback kind of mechanisms. Those are in fact the most effective way to get things to happen. You don't have to do it on every single provider in the United States. You can pick subsamples of them, and you pick them randomly, and the DEA can control that also.

I think when they go into that, you'll get process measures. The problem is we're looking at outcomes, outcomes that are often a couple of years out; process measures, that is finding providers who don't do what they're supposed to do, including getting the training. You can figure that out usually within months. Again, I base that on experience out of a system in the VA that's big and national, and we do it.

I'm afraid I just see backpedaling for very easy things, when in fact, there are harder things to do, perhaps, but they need to be done. And there needs to be process measures. That would be feedback comes back sooner. They are different metrics than we've been discussing. And I think death and these

other kind of metrics are perhaps convincing and hard outcomes, but they're disastrous. I don't know why we're settling for outcomes that have to be so Draconian, when there are other ones that you can, and you can identify who are the problematic providers, and you can do something about them.

DR. KIRSCH: Dr. Kerns.

DR. KERNS: Just briefly, I get excited about this question because of specific interests in evaluation and methods. I think that there are opportunities here for specific partnerships, interagency partnerships, and including, in particular, NIDA and maybe other institutes.

I think, in fact, disagreeing with Dr. Farrar's conclusion about E, that it's impossible to do, I think that, in fact, well designed, mixed method, qualitative, quantitative approaches that are focused in more specific areas, a specific catchment area, a county here and there to study the effects of REMS in the context of other changes, and looking at collecting data from a variety of stakeholders, both quantitative and qualitative data, is the kind of

research that really could help inform, give answers to some of the questions that we're struggling with today and help inform future efforts in this direction.

So without being really specific, I think there are a lot of empirical questions embedded here and looking not only at more sophisticated modeling approaches to the data that we already have and trending those into the future, creating new -- I don't know if the answer is registry, but metrics. Population-based metrics would make sense, but also focused science, again, through our partnerships with the NIH would make sense to me.

DR. KIRSCH: I'd like to maybe provoke the committee a little bit. And as I listened to the comments, I hear about metrics over the outcomes of a REMS program, as far as whatever bad outcomes exist from this class of drugs or these classes of drugs, and the other metrics being around providers.

I think they are a bit different, and I think the committee is split on the idea of having registries that involve individual patients or

individual providers, or looking at more global data to look at an overall effect of a program. And I'd like to ask for a comment from the committee about is there a consensus or not about whether we recommend individual metrics about individual patients or providers versus a global evaluation of the program.

Dr. Ballantyne.

DR. BALLANTYNE: Well, I was just going to say that in addition to everything that's already being done -- I mean, there are a lot of processes for measuring these bad outcomes of opiate treatment, that the prescription monitoring system's absolutely vital in where we can go next. And prescription monitoring systems are actually de facto registries, and they do give us the information we need. And the existing prescription monitoring systems, as far as I know, not all of them make the information available to physicians. I don't think they do in Pennsylvania.

So I can't find out who else is prescribing to my patients, for example, and if I could, it would be very helpful. But I think prescription monitoring is a direction we need to go, and it does actually

produce some form of registry of patients and prescribers.

DR. KIRSCH: Dr. Turk.

DR. TURK: I think we may need to make a distinction between what are we predicting, what are the outcomes we're trying to change, and what are the metrics we're going to use to look at what the predictors are.

We know or we have some sense of the types of outcomes we're looking for, ultimately, which is we want to reduce morbidity and mortality, so say with opioids. So in one sense, it's like what are those outcome metrics, and then we could say what are the process metrics that will allow us to see if they affect or influence or predict what those outcomes are.

So I think we're mixing the dependent and the independent variables here to some extent. And I think, if we agreed on what the dependent variables are, then we could begin to start talking about what would be the metrics we would use to collect the independent variables.

For example, knowing the number of physicians who prescribe in a certain way, does that predict a change in the outcomes we're concerned about? Have we agreed on what the metrics are for the outcomes? I think that's where we have some problems, because the RADARS and the DAWN and all the data that we've seen, each of them have significant problems with them that have been identified and pointed out to us. And the question is, do you make use of those existing systems because they exist and we have prior information so we can track things? Do you do that in addition to or instead of trying to develop some new outcome measures, as Dr. Farrar was talking about? I think that's a decision that has to be made.

At a minimum, I think, at least in my opinion, we should take the existing metrics we have and make use of them at the same time while thinking of alternatives to those, and then begin to look at what would be the variables that would predict changes in those types of outcomes, physician prescribing, types of prescriptions they're engaging in, and the amount of education that's provided, the numbers that

opt in and opt out. Those would be the independent variables to predict the outcomes that we're interested in.

DR. KIRSCH: Dr. Kerns.

[No response.]

DR. KIRSCH: I'm going to try to summarize this as best I can, and just to warn you, we have several members of the committee who got together and put together a statement that we're going to project and ask for your thoughts about the statement to send maybe a clearer message to the FDA.

So with regard to discussing the assessment, how to assess the impact of the REMS, I think that the consensus of the committee is that we would want to make use of all the existing outcome measures that we've seen presented over the last two days now. But in addition to that, develop new outcomes, as Dr. Farrar had mentioned, but not lose track of the existing outcomes in order to be able to truly determine whether or not there's a positive or not a positive effect of the interventions that we've suggested.

The specific metrics that should be used in sources for data on those metrics, again, like I just said, we want to use existing databases, although some of those are delayed in their reporting. I think the committee agrees it would be a mistake to throw that data out, but at the same time, determine new variables that would more specifically address the outcomes we're trying to look at in the way of more than just mortality, but the morbidity as well.

I think the committee as a whole would prefer not to have specific registries. The changes in those metrics that would suggest a need to make changes in the REMS, I think, if morbidity and mortality improve, that would be a good thing. The appropriate period of follow-up for initial evaluation to determine if the REMS is working, although I think if the new metrics that may be developed could be followed on a very frequent basis, certainly the existing metrics would take months and maybe even years to determine whether or not there was a positive effect of the REMS.

I personally -- I shouldn't give my personal

opinion, but because of the type of data we're talking about, I think the sense of the committee is that we would want to look at the data over a period of at least quarters to years to see whether or not the impact of the intervention is effective or not.

Anyone want to add to that?

[No response.]

DR. KIRSCH: Amazing.

Yes, Dr. Krantz?

DR. KRANTZ: Just a small comment. I think what was most disturbing to me was that we really can't look at mortality, which is the elephant in the kitchen, until four years. As you recall, the last data we have of the 14,000 deaths was 2006. It's 2010, as I looked today.

So one question I had is can we use the surrogate marker of emergency room visits, that we can get from RADARS, as you mentioned, or other sources, as a way to give us an inclination of where we're going towards, if we believe that most of these are poisonings and not, indeed, cardiac deaths. So I think that would be a useful tool to use.

The other thing I wanted to bring up to the Office of Epidemiology and Surveillance, is there any way we can look at state-level data and not have to wait for the CDC to do their amalgamation over a four-year period? That could give us a quicker signal.

DR. KIRSCH: Dr. Dormitzer.

DR. DORMITZER: The emergency room data is collected by SAMHSA, and that usually is about like a nine-month lag after the year has ended. So 2009 will be released in September of this year. I can ask for state -- we can get state-level data. And SAMHSA also collects mortality data. But I think they collect six, six or seven states, and so I can get data for those states. It's on substance. So it's going to be oxycodone, hydrocodone, methadone. It's not going to be extended release or immediate release. That's what mortality will not give us.

DR. KRANTZ: Just as a clarification, is the SAMHSA data limited to the OTP environment, which is a separate, regulatory issue, if you will?

DR. DORMITZER: SAMHSA? No. SAMHSA provides emergency room visits.

DR. KRANTZ: Okay. So it's not just the OTPs? Okay.

DR. DORMITZER: For methadone, it's both OTP and analgesic methadone.

MS. WILLY: I had a comment. This is Mary Willy from DRisk. We've also talked with vital statistics, Dr. Anderson, who was speaking yesterday about the possibility of getting access to earlier data from the states. Some states, as you've heard, have the data sooner than others. So we're exploring that as another possibility.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: I just wanted to mention to add to it something that I'd mentioned before, too, is that we really didn't see any error data, preventable error data in the FDA error system. And that is something else that I think you should also track. And on a dynamic basis, too, you may be able to look for different outcome metrics that you want from the data that's in there. But I should at least mention to put that into the database to look at it. It may not be quantitative, but it should be good data.

MS. WILLY: To your point, we have been working with the folks at CDC, and they do collect information, the nice CAIDS, specifically about medication error. So we're exploring that, as I mentioned yesterday.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: I just wanted to add to what you had summarized in the sense that we've spent a lot of discussion around physician measures. And I just wanted to make sure that there's an equal amount of discussion around metrics that relate to the patient knowledge and behavior. So I actually wanted to endorse -- the FDA had a nice conceptual framework of how they laid out knowledge, behaviors, and outcomes that I think might be a useful way to map many of these measures. And to that, we should also be adding behavioral intent and attitude mapping, because those are things that are predictive of eventual behavior.

Then, in addition to the quick pharmacy audits that were mentioned by Dr. Farrar, there's also a technique where you can be doing home audits, medicine cabinet-kind of audits, either via survey or

telephone. For instance, the National Asthma Survey collects information about what kind of medicines that they're using. They allow patients to bring the medicines to the phone, and you can get information about, really, what is safe use, storage, and proper disposal, and get an audit of that. That I think would help complement knowledge, too.

DR. KIRSCH: Thank you.

Dr. Kosten.

DR. KOSTEN: Thank you. I wouldn't want to lose track of it. We do have a lot of surrogate measures that are, in fact, quite relevant to this, which is all the drug abuse data. I mean, we have monitoring the future. Those tend to be much earlier markers than deaths, of where you have a problem. And I think that you can look at how much the drug's being abused in all these various surveys. And if you have that by particular types of compounds, you can usually pick up trends over time, if nothing else, to identify which drug is problematic compared to others.

So we just don't seem to be mentioning that much, but yet, that is an outcome measure. It's

readily available, collected every year, tends to get a relatively small lag time compared to some of these other measures.

DR. KIRSCH: Thank you.

Dr. Boyer.

DR. BOYER: In regard to the question as to whether or not the emergency department data can be used, I think the answer to that is going to be no. DAWN is based on mentions, which functionally means that if a particular drug is mentioned in the chart, then it is a mention, whether or not the presentation was actually related to that drug use or not.

The Poison Control Center Data, we know that there are dramatic underreportings to poison control centers, particularly for drugs like opioids, which are relatively easy for emergency physicians to manage. So they don't call in either for reporting because they're so mundane or because they need assistance and treatment because the management for someone who can be resuscitated is relatively simple.

Even in poison control center data, where we were kind of surprised recently, looking at missing

data rates, even when specialists, the people who collect the data in poison control centers, were told to look for specific drug presentations, the missing data rate for those drugs, where they're looking for information specifically, was about 80 to 85 percent And then that data gets fed to RADARS, which functionally is a contract research organization. And how you manage the missing data on its way to analysis, I think, is a very, very real question, considering the sources of the funding.

DR. KIRSCH: Dr. Hatsukami.

DR. HATSUKAMI: I just want to reiterate what Dr. Morrato said, which was the importance of assessing attitudes, knowledge, and behavior of not only the prescribers, but also the patients. And on top of that, I think it's important to consider measuring those areas within members of the community as well, because it appears that education of the community was a significant part of the Safe Use Initiative. And unless we have campaigns that are effective, why use the money, in terms of continuing campaigns, which are not effective?

So I think a critical component is to assess community attitudes and behaviors.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: It was said already. But I also was going to add to what Dr. Kerns has said. NIDA does have -- to put in a little plug for my organization -- we do have some pretty extensive data network in addition to the excellent data networks that SAMHSA has, monitoring the future. It was mentioned, and it is considered a good measure for future use.

Also, we have a community epidemiology work group, which is sort of a community-based level of individuals who in treatment centers and other community areas, when they hear of an outbreak of fentanyl in Houston, it’s put up and it’s explored right in real time.

In addition to some very experienced researchers in the field like this, we do have ways to augment some of the data that was mentioned and to use all the federal partners, I think would be more than willing to assist in any way possible on this very

significant topic. Thank you.

DR. KIRSCH: Thank you.

So this is a statement that was developed by some members of the committee. And I thought it was worthwhile, with permission of the FDA, to potentially discuss and endorse, or not, the statement. I'll read it.

"It is the clear sense of the committee that the problem of opiate abuse and misuse are present public health concerns. The REMS process, as defined by FDAAA, has a limited effect, as it fails to address many of the root causes of the problem.

"The FDA REMS process lacks critical regulatory authority with regard to mandated training, enforcement, and coordination of data acquisition, that are key components of any process that is likely to impact this most important public health issue.

"The committee strongly recommends that legislation be developed that allows for a coordinated interagency approach that includes input from FDA, DEA, ONDCP, and other stakeholders inside and outside of government."

Comments? Dr. Terman.

DR. TERMAN: I just wanted to ask about the possibility that arose earlier about takeback programs or buyback programs.

Are there other stumbling blocks that aren't listed there in terms of coordination of such programs? I just don't have enough knowledge to know that.

DR. THROCKMORTON: Are you asking specifically --

DR. TERMAN: I'm asking if there are other agencies in the federal government that would be useful to list there if we were interested in suggesting such programs.

DR. THROCKMORTON: A couple things. First off, it'd be interesting to hear a little bit more about how the second paragraph relates to the first paragraph. As I read it, just for this first time, it's saying the REMS authority is limited, and then, that where necessary, you should seek legislative changes to enable cooperation with other federal partners.

Is that sort of roughly the message that you're intending to send with these two things? I'm not trying to put words into your mouth. I'm just trying to understand. Because there are many examples of coordinated work between FDA, DEA, and ONDCP, SAMHSA, NIDA, CDC right now that don't require legislative change, that are sort of happening day to day. There are specific things like takeback programs for controlled substances, where, at least I'm told -- not being a lawyer nor wanting to try to be one -- that legislative changes are required.

So the intent is to focus on that latter piece, as I'm understanding it, focus on the places where legislative changes are needed to accomplish those intergovernmental co-operations.

Is that fair?

DR. KIRSCH: Add in the statement "as required"?

DR. THROCKMORTON: "Where necessary," or something, because in the specific issues of drug takebacks -- as Dr. Jenkins has said, in the specific issue of using the DEA, the existing DEA registration

system as a part of the things we've discussed, those things would require legislative change. Many other activities I would say would not.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: I think what Doug is saying, that you don't need legislation to coordinate with other agencies. We already have that. And what you've added now -- and it could be maybe even a little clearer -- is that to augment the REMS program, additional legislative authority has to be granted, A, to FDA, and to other agencies, such as DEA, to be able to carry on those pieces that can't be carried on now.

DR. KIRSCH: Dr. Covington.

DR. COVINGTON: Well, I agree with what you just said. And if it's likely that somebody is going to be listening to this, it might be more useful if we had a unanimous vote on it when we get it reworded.

DR. KIRSCH: Yes. The intent is to vote.

Dr. Denisco? Please use your microphone.

DR. DENISCO: I'm sorry. Thank you.

I think that we could get bogged down, or a future group could get bogged down, where we say

recommends that legislation be developed that allows for coordinated approach. That exists already; rather, that the committee strongly recommends that a coordinated interagency approach be continued, and not mention any specific organizations, like the DEA and ONDCP, because the variety of federal agencies that are involved, there's environmental protection that had to be involved with flushing drugs down the toilets.

So it becomes really limiting. So say that this should be continued, and that, where specific legislation be required, this should be -- whatever -- this should be sought by the specific agency involved.

DR. KIRSCH: Do you believe that the comment, "And other stakeholders inside and outside of government," captures those groups?

DR. DENISCO: I think the emphasis on DEA and ONDCP is excessive.

DR. KIRSCH: Dr. Kerns?

DR. KERNS: It seemed to me that we're converging on the idea that it's not about coordinated legislation to allow coordinated interagency approach;

it's about it addresses limitations in the current legislation to address some of the concerns that we've raised in this group. So it's to address current limitations in the law.

I guess I'm recommending for, "The committee strongly recommends that legislation be developed that addresses current limitations in the law," maybe, "especially involving interagency collaboration" or something like that. But I don't even think that's necessary.

DR. KIRSCH: Okay. Any other suggestions?

Dr. Peairs?

DR. PEAIRS: I'm just wondering if the second paragraph is accurate. I think the FDA REMS process does have authority for mandated training. It's that this particular proposal lacks those items, unless I'm reading that wrong.

DR. KIRSCH: I think the emphasis is the process as defined currently.

DR. PEAIRS: For this particular proposal?

DR. KIRSCH: Yes.

DR. PEAIRS: Okay.

DR. KIRSCH: That's what we're asked to comment on.

Dr. Kosten?

DR. KOSTEN: Just, I hope we can get some input from the FDA and other places, because there is a law on the books already -- this may simply reflect my age -- that not only allows but asked for interagency agreement, that interagency agreement has not been in effect for -- it may be even 15 to 20 years now. It was dissolved. But the law is still on the books, as far as I know. And now, there may be enforcement authorities that I'm hearing about, that the DEA has, that the FDA doesn't have, with providers. But when it says, "current limitations in the law," it would be sure nice to say what are those limitations.

I don't think there's any specific limitations across these agencies getting together, and in fact, I think there's a law that encouraged that. Now, why they stopped doing it is another question, but there are enforcement restrictions in here that only the DEA can do. So I would like to

actually have -- if we're going to say something like this, to have a lawyer who knows the laws and prove this for us. And that's an FDA request that I would make.

DR. KIRSCH: Now, remember, our committee is advisory, not prescriptive. And what we write here, I trust, if the FDA takes to heart, or the public takes to heart, will not be the final language that's used in any sort of legislation. So I think the purpose of this is to send a clear message to the public, and to the FDA that we urge interagency interaction to solve this problem.

DR. KOSTEN: I think it's always nice to look like you knew what happened in history, is all I'm saying.

DR. KIRSCH: Thank you.

Dr. Krantz?

DR. KRANTZ: I just had one small worry about the premise of the first paragraph. I mean, in essence, what I thought I heard this committee say is that they want to use the existing REMS system, tighten it up, strengthen it, create a more

restrictive REMS, if you will. And by sort of claiming that it's unhelpful is that sort of sending a message that we don't want to use that vehicle. That was one unintended consequence I'd be concerned about.

Then, I guess if it's something we want with the DEA for registration, I would simply suggest we be as declarative, as Dr. Kosten said, as possible.

DR. KIRSCH: Dr. Bickel?

I'm sorry. Dr. Denisco?

DR. DENISCO: When I read it now, "The REMS process as defined by the FDA will have a limited effect," the REMS process, it's not clear.

Is it the REMS process in general or is it as presented today? It's getting unclear to me. And that "The FDA REMS process lacks critical regulatory authority," we're not sure that it does. We're just saying that the REMS that was proposed had some limitations that we wanted to address.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: So wordsmithing any document, even five or ten sentences in a large group, is difficult. My sense of this is that we've heard

for two days that this committee sees this as a bigger problem than the authority that the FDA has to regulate. And there are certain comments made by every one of us that address the hope that we could do something about the problem.

At various times, we've heard both representatives of the FDA and us say that there needs to be authority that either needs to be granted to the FDA or to the DEA or to any other alphabet soup in the government.

What I heard from the committee members, all of us sitting here, was that we thought this was an important enough problem that we needed to make a statement that said the committee really recommends further action than just the REMS issue that we're discussing today.

I think we can make a simple statement. And I'm hoping that, as we're wordsmithing this, that it becomes simpler rather than more complicated, to give the appropriate impetus and a public statement that we take this seriously, and that we expect our federal government to respond in an appropriate manner. And

if the FDA has taken this on -- and I applaud them for bringing this to our attention and to the public again -- then we need to help them address the issues in a timely manner.

DR. KIRSCH: I believe that when we voted and went around the table, and each gave our opinions, we each, in our own way, emphasized many of these same issues. So because of the comments that you made about how difficult it is to wordsmith this with such a large group of people, and if we're going to present it to the FDA and to the public as the opinion by this committee, I think it would not do it justice to do it in that fashion.

So I think all of our comments were made as part of the public record, and we said in our own way our feelings about this. So I think it's best to be left alone. Unless there's otherwise strong opinion. I will adjourn the meeting.

(Whereupon, at 3:33 p.m., the meeting was adjourned.)